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Agitation, Sedation, and Delirium in Adult ICU Patients

Includes 5 Pharmacotherapeutic/Pharmacology Hours

This course meets 1.5 hours of pain management education and .5 hours of opioid/controlled substance education.

Audience
This course is designed for nurses, physicians, and physician assistants involved in the care of patients in intensive care units.

Course Objective
The purpose of this course is to provide prescribers and other healthcare professionals with the knowledge and skills necessary to identify and act to avoid or address agitation, inappropriate sedation, and delirium in ICU patients.

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

1. State the principles of analgesia and sedation in ICU patients.
2. Describe appropriate care of ICU patients receiving opioids.
3. Compare sedatives commonly used in ICU patients.
4. Review monitoring requirements in ICU patients receiving sedatives.
5. Discuss the prevention and management of delirium in ICU patients.

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Faculty Disclosure
Contributing faculty, Beth Johnston, PharmD, BCPS, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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

INTRODUCTION

Agitation (characterized by excessive motor activity) is common in critically ill patients, with an incidence of between 16% and 71% [1; 2]. It is reported as severe in 16% to 46% of these patients [1; 2]. Appropriately preventing and treating pain, anxiety, delirium, immobility, and sleep disruption can improve outcomes for these patients [2; 3]. Treatment goals should include both physical and psychological comfort while also keeping patients safe and allowing them to receive needed care [2; 3]. It has been established that minimal sedation that results in comfortable wakefulness improves clinical outcomes [1].

There can be many reasons for a critically ill patient to be agitated. Pain, anxiety, and delirium are three of the most common causes. Other causes can include [1]:

- Drug withdrawal (e.g., nicotine, alcohol)
- Endotracheal tube
- Fear
- Infection (central nervous system, sepsis)
- Ischemia (myocardial, intestinal, cerebral)
- Metabolic (acidosis, hypoglycemia)
- Respiratory failure (hypoxemia, hypercarbia)
- Sleep-wake-cycle disruption
- Tension pneumothorax
- Uncomfortable physical position/immobility

Some of the overarching principles of the Society of Critical Care Medicine (SCCM) guidelines for the management of pain, agitation/sedation, delirium, immobility, and sleep disruption (PADIS) in adult intensive care unit (ICU) patients are [3]:

- Pain, depth of sedation, and delirium should be routinely monitored.
- Pain should be addressed first and treated adequately and pre-emptively.
- Sedation should be provided only if it is needed.
- Light sedation is preferred so that patients are aware and responsive.

Mobilization and/or rehabilitation (in- or out-of-bed) of patients in the ICU may be effective in reducing ICU-acquired muscle weakness as well as a tool for delirium prevention. Sleep disruption, common to ICU patients, may contribute to delirium, prolonged mechanical ventilation, altered immune function, and neurocognitive dysfunction [3].

The SCCM, through the ICU Liberation Collaborative, has developed the evidence-based ABCDEF (also known as the ICU Liberation bundle or A2F bundle) care bundle as a quality improvement initiative [4]. The components of this bundle are:

- A = Assess, prevent, and manage pain
- B = Both spontaneous awakening trials (SAT) and spontaneous breathing trials (SBT)
- C = Choice of analgesia and sedation
- D = Delirium (assess, prevent, manage)
- E = Early mobility and exercise
- F = Family engagement and empowerment

The goal is to use this methodology, so patients are awake, engaged, and mobile. In this model, the ICU team works with patients and family members as partners [4].

Both sedative and analgesic agents are commonly administered to critically ill patients [5]. The following questions can be addressed to help optimize the management of these patients and to prevent the inappropriate use of analgesics and sedatives in critically ill patients [5]:

- Are both sedative and analgesic drugs needed?
- Does the patient have one or more factors that could cause drug accumulation (e.g., kidney or liver impairment)?
- If analgesic and sedative drugs were required and started, are these drugs still needed and are the doses still appropriate?

Patients who receive optimal analgesia and sedation have less pain and anxiety, which allows for invasive procedures, reduces stress and oxygen consumption, and improves synchrony with mechanical ventilation [2; 6; 7]. Providing an appropriate level of analgesia and sedation to ICU patients in particular can improve patient outcomes, including duration of ICU stay and duration of mechanical ventilation [2; 6]. However, a large number of critically ill patients do not receive optimal analgesia and sedation.

ANALGESIA IN ADULT ICU PATIENTS

REFLECTION

How do your patients define pain? What tools can be used to assess pain in critically ill ICU patients who may not be cognitively responsive? What are the goals of pain therapy? What strategies do you use to optimize pain control while minimizing the adverse effects of pain medications?

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" [8]. This definition emphasizes the fact that pain is subjective and that it can exist solely because the person experiencing pain reports it [9].

Pain in adult patients in the ICU has been identified as a great source of stress [1; 3]. The resultant catecholamines that are released into the circulation can negatively impact the patient's condition. Patients may experience arterial vasoconstriction, impaired perfusion to tissues, and reduced tissue-oxygen partial pressure. In addition, pain can cause catabolic hypermetabolism (e.g., hyperglycemia, lipolysis, breakdown of muscle). These effects can impair wound healing and increase the risk of wound infection. Acute pain is an important risk factor for the development of debilitating chronic pain (often neuropathic pain) [3].

Inadequate pain control is often reported by patients discharged from an ICU [3]. Both medical and surgical patients with memories of pain and trauma years after an ICU stay are at increased risk for chronic pain and developing post-traumatic stress disorder (PTSD) [9].

CAUSES OF PAIN IN THE ICU SETTING

Patients in an ICU are likely to experience pain regardless of their diagnosis. It is not uncommon for some pain to go unrecognized and/or untreated. Critically ill patients can experience pain at rest, from common things such as a nasogastric tube, intravenous (IV) lines, or lying in the same position for too long. An endotracheal tube is an important cause of discomfort and pain in ICU patients. An ICU patient's pain may be secondary to surgery, trauma, burns, or cancer [2; 3]. Procedural pain is also common in these patients.

DETERMINING IF A CRITICALLY ILL PATIENT IS IN PAIN

The potential inability of adult ICU patients to communicate verbally cannot be interpreted to mean that they are not in pain. Proper assessment, and subsequent treatment, of pain is crucial due to the negative physical and psychological consequences that can be seen during a patient's hospital stay and after discharge. Identifying pain and treating it early is preferred and more effective than delaying treatment until the pain becomes severe. In fact, pre-emptive analgesia is recommended for potentially painful procedures such as chest tube removal and wound care [3].

All patients in the ICU setting should be evaluated for pain. Vital signs, such as heart rate and blood pressure, can suggest that a patient is in pain. However, vital signs alone should not be used for pain assessment in adult ICU patients, as these can be confounded by underlying conditions or medications (e.g., vasopressors, inotropes) [10]. Although a patient's own report of pain is the best evaluation, critically ill patients are often not able to communicate [3]. The Critical-Care Pain Observation Tool (CPOT) is one tool that is recommended for medical, postoperative, and trauma patients who are not able to self-report [3]. This tool includes four categories: facial expressions, body movements, muscle tension, and ventilator compliance or vocalizations for extubated patients [11; 12]. The Behavioral Pain Scale (BPS) is another tool that is recommended for adult ICU patients who are unable to communicate verbally. This scale has three items of assessment: facial expression, upper limb movements, and compliance with mechanical ventilation [12; 13]. This tool is available for both intubated and non-intubated patients [3].

Other examples of pain scales used in the ICU include [1]:

- Numeric Rating Scale (NRS): patient-reported pain, range 1 to 10, target <4
- Critical Care Observational Tool (CPOT): observational, range 0 to 8, target <3

DRUGS OF CHOICE FOR TREATING PAIN IN CRITICAL ILLNESS

What is the best approach to manage pain?

The benefits of analgesic agents for pain control in critically ill patients must be balanced with the risks associated with the medications themselves (e.g., respiratory depression, hemodynamic compromise, addiction potential) [6]. In addition, too much or too little analgesia can increase risks such as nosocomial infections, delirium, prolonged duration of mechanical ventilation, and increased duration of ICU and hospital stay [2].

Patients in the ICU have less predictable pharmacokinetics and pharmacodynamics than non-critically ill patients due to hemodynamic instability, altered protein binding, drug interactions, and impaired organ function [6].

Nonpharmacologic methods, such as relaxation, massage, music therapy, lumbar support, injury stabilization, application of cold, and repositioning, can help improve patient comfort and decrease pain [2; 3; 6]. However, these methods are considered complementary in critically ill patients and are unlikely to completely control pain [6].

Non-Opioid Analgesics

Non-opioid analgesics, such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen, ketorolac), may be used in adult ICU patients as part of multimodal pharmacotherapy [3]. These can be considered adjuncts and most appropriate for the treatment of less severe pain. They are recommended for use in addition to opioids to help reduce opioid requirements (i.e., opioid-sparing) and opioid-related side effects, improve pain control, and improve patient-centered outcomes [3; 6].

Acetaminophen should be avoided in patients with significant liver dysfunction. Further, clinicians should exercise caution with NSAIDs in patients with kidney dysfunction, heart failure, cirrhosis, gastrointestinal bleeding, or platelet abnormalities [14].

Various medications (e.g., tricyclic antidepressants, gabapentin) are recommended for the treatment of neuropathic pain [3]. Monotherapy with IV opioids is not recommended in the treatment of neuropathic pain [3]. In some cases, gabapentin, pregabalin, and carbamazepine are used as opioid-sparing agents in critically ill adults.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Society of Critical Care Medicine suggests using nefopam (if feasible) either as an adjunct or replacement for an opioid to reduce opioid use and their safety concerns for pain management in critically ill adults. (https://www.sccm.org/Clinical-Resources/Guidelines/Guidelines/Guidelines-for-the-Prevention-and-Management-of-Pa. Last accessed January 25, 2024.)

Level of Evidence: Very low

Ketamine

Ketamine may be a safe and effective option in select ICU patients [14]. Ketamine seems to work as well as opioids for acute pain. (Note that pain doses are much lower than those used for sedation/anesthesia.) However, there are still potential side effects, such as nausea, mild hallucinations, and confusion. In addition, limited safety data exist for higher-risk patients, including those with schizophrenia or with decompensated heart failure, as ketamine may increase heart rate or blood pressure. Clinicians may consider using ketamine to reduce opioid needs or to consider ketamine as an alternative if opioid use may not be safe [15; 16].

It is important to adhere to hospital protocols for ketamine use, including contraindications, as these may vary among facilities. Examples of contraindications include:

- Risk for psychotic behavior, such as schizophrenia or alcohol withdrawal
- History of severe allergic reaction to ketamine
- Increased intracranial or intraocular pressure
- Hypertensive emergency
- Decompensate heart failure
- Cardiac ischemia
- Uncontrolled cardiovascular disease (e.g., heart failure [during acute decompensation], acute coronary syndrome)

Emergence reactions with ketamine appear to be rare, especially with the lower doses used for pain. Reactions may involve anxiety, delirium, dream-like states, nightmares, illusions, or visual hallucinations [15; 16].

Clinicians should consider warning patients about the potential for emergence reactions; this may improve acceptance [15; 16]. Emergence reactions may not be as common with lower doses or in those older than 65 years of age, but caution is still warranted. Patients who are given ketamine should be provided with an appropriate environment and minimal stimuli during recovery to minimize emergence reactions. This may include dim lighting, limited noise, and have a comforting person present.

Lidocaine

Intravenous lidocaine is also sometimes an option for refractory acute and chronic pain syndromes, such as renal colic, neuropathic pain, and headaches. In addition, lidocaine is used perioperatively to limit opioids and hasten recovery [17].

However, lidocaine is not appropriate in all patients. For example, IV lidocaine should not be combined with regional anesthesia due to the increased risk for local anesthetic systemic toxicity [17]. IV lidocaine is contraindicated in patients with cardiac conduction abnormalities (including Adams-Stokes or Wolff-Parkinson-White syndromes) and severe sinoatrial, atrioventricular, or intraventricular block [17]. It should also be avoided in patients with seizure disorders, due to seizure risk with supratherapeutic blood levels of lidocaine [17].

Opioid Analgesics

Opioids are recommended as first-line agents for treating non-neuropathic pain in adult ICU patients due to their combined analgesic and sedative properties [2; 3; 6]. Respiratory depression from opioids is common, as well as hypotension secondary to a decrease in sympathetic tone or vasodilation from histamine release. Opioids can also cause decreased gastrointestinal mobility, pruritus, flushing, urinary retention, and delirium [6]. The adverse effects of opioids can increase a patient's length of stay in the ICU and worsen post-ICU outcomes. Efforts should be made to use non-opioid analgesics as well as nonpharmacologic methods to reduce opioids to the lowest effective dose for the shortest period of time [3].

All IV opioids are considered equally effective when titrated to achieve similar pain intensity endpoints [3]. The appropriate agent should be chosen based on its pharmacokinetics, metabolism, and adverse effect profile. Also consider if the patient is opioid tolerant.

Potential adverse effects to consider when using opioids in patients in an ICU include:

- Depressed consciousness
- Hallucinations
- Hyperalgesia

COMPARISON OF OPIOIDS COMMONLY USED IN CRITICALLY ILL PATIENTS			
Drug	**Onset (IV)**	**Half-Life**	**Comments**
Fentanyl	1 to 2 minutes	2 to 4 hours	Less hypotension compared with morphine Accumulates in liver impairment
Hydromorphone	5 to 10 minutes	2 to 3 hours	Accumulates in kidney and liver impairment
Morphine	5 to 10 minutes	3 to 4 or 5 hours	Accumulates in kidney and liver impairment

Source: [20] *Table 1*

- Hypotension
- Ileus and constipation
- Increased intracranial pressure
- Nausea and vomiting
- Peripheral vasodilation
- Pruritus
- Respiratory depression
- Urinary retention
- Withdrawal

The primary opioids used in critically ill adult patients are fentanyl, morphine, and hydromorphone (***Table 1***) [3; 6]. Meperidine is not generally recommended due to the risk for neurologic toxicity (e.g., reduction of seizure threshold) [9].

Continuous opioid infusions may be used for ongoing pain, as well as for moderate or severe pain that is not relieved by intermittent injections. Intermittent, or bolus, injections are also useful for moderate pain and for preprocedure analgesia prior to and during painful procedures such as dressing changes. If a patient is conscious, they may be able to use patient-controlled analgesia (PCA) to control their pain by self-administering bolus injections as needed, with or without an underlying continuous infusion. All infusions and doses should be monitored closely and titrated as needed to give optimal pain relief while avoiding oversedation and unwanted adverse effects.

Fentanyl is commonly used for continuous pain control. It has a relatively short half-life (two to four hours), which makes it easily titrated when given as a continuous infusion [6]. Fentanyl is metabolized in the liver, has no active metabolites, and may accumulate in patients with liver impairment [9]. Fentanyl is lipophilic and may accumulate in fat and muscle with prolonged infusions, increasing the half-life in patients with obesity [6]. The accumulated drug may be released after the infusion is stopped, leading to prolonged activity. However, fentanyl is often preferred because it does not undergo elimination via the kidney. Fentanyl also causes less hypotension than morphine.

Morphine and hydromorphone can be used as continuous infusions but may be chosen for intermittent IV injections because their half-lives are longer than fentanyl [6]. Morphine and hydromorphone are metabolized by the liver, and the metabolites are excreted by the kidneys. Their effects can be prolonged in patients with liver or kidney impairment [6; 9].

Morphine has a half-life of 3 to 5 hours, with an onset of analgesia of 5 to 10 minutes. It has a moderate volume of distribution, and its effects can be prolonged in obese patients [6]. Morphine causes histamine release, which can result in hypotension, itching, flushing, and bronchospasm [6; 7; 19].

Hydromorphone is much more potent than morphine. It has an inactive metabolite that may cause neuroexcitatory symptoms, especially for patients with kidney impairment, in which there can be accumulation with repeated doses [18].

Remifentanil is a derivative of fentanyl. It is metabolized by blood and tissue esterases and does not accumulate in patients with kidney or liver impairment. Remifentanil has a very short half-life (shorter than fentanyl) of 3 to 10 minutes and should not be used for bolus dosing alone [6]. It may be preferred for patients who need prompt reversal of action (e.g., requirement for frequent neurologic assessments). Remifentanil should be dosed on ideal body weight, or adjusted body weight in obese patients [3; 6]. Fentanyl and remifentanil are equal in terms of achieving sedation goals with no difference found in a patient's duration of mechanical ventilation [6]. However, the use of remifentanil in the ICU setting seems limited by its high cost and its association with hyperalgesia following discontinuation of infusions [6; 7]. Despite the theoretical advantages of remifentanil, more evidence is needed to solidify its place in therapy for analgesia and sedation in critically ill patients [2].

Sufentanil has a quick onset of one to three minutes, similar to fentanyl. It should not be used for bolus dosing alone. Sufentanil has no active metabolites, and its clearance is not affected in patients mild or moderate kidney impairment [9]. The dose should be based on ideal body weight if the patient's actual weight is more than 120% of ideal body weight [21]. For patients without IV access, sufentanil is also available in a sublingual formulation that is administered by trained staff. However, it is more expensive than other opioids and there are not data to prove it is more effective. For patients without IV access, hospital protocols should be followed for other opioid administration routes; for example, fentanyl injection can be given intranasally.

Constipation Management

Patient A is a new trauma patient receiving scheduled and as-needed opioids while immobile and recovering from multiple surgeries. Which type of laxative would be appropriate for this patient?

All patients receiving opioids should be on an effective bowel regimen. It is important to initiate bowel regimens when the opioid is started instead of waiting for symptoms to develop. Bowel regimens typically include a scheduled osmotic (e.g., polyethylene glycol [PEG] 3350) or stimulant laxative (e.g., bisacodyl). These two can be combined if necessary. Other medications, such as magnesium citrate, glycerin suppositories, or enemas, can be added on if these are not effective. Although adding a stool softener (e.g., docusate) to a stimulant laxative is widely recommended, small studies show that this approach is not beneficial [59; 60].

The bowel regimen should be individualized based on patient characteristics and special considerations. Unique considerations include [22]:

- Avoid bulk laxatives in patients who are immobile, on fluid restriction, or have difficulty swallowing.
- Avoid oral laxatives in patients with an intestinal obstruction.
- Use enemas or suppositories for patients with fecal impaction.
- Use an osmotic laxative (e.g., PEG 3350) for patients who should avoid straining, such as after surgery or myocardial infarction.
- Avoid saline laxatives (e.g., magnesium-containing, oral sodium phosphate) in patients at risk for electrolyte abnormalities (e.g., concomitant diuretics, elderly, heart or kidney failure).

Addressing Opioid Tolerance

Treating acute pain in patients taking chronic opioids can be challenging. For example, postsurgical or trauma patients often need large doses to control pain, which can be outside of some clinician's comfort zone [23]. When selecting or evaluating pain regimens, ensure surgical patients continue their usual maintenance regimen before surgery to prevent withdrawal and uncontrolled pain and verify that as-needed doses are adequate based on the scheduled regimen [23]. The oral route is preferred, but if the patient cannot take their usual maintenance regimen (e.g., post-operatively), consider converting it to basal rate PCA. It is important to avoid escalating the patient's long-acting opioid regimen and to avoid long-acting opioids or fentanyl patch for acute pain. When selecting doses, consider potency differences among opioids [23].

OPIOIDS BY STRUCTURAL CLASS	
Structural Opioid Class	**Specific Opioids**
Morphine group	Buprenorphine Butorphanol Codeine Hydrocodone Hydromorphone Levorphanol Morphine Nalbuphine Oxymorphone Oxycodone Pentazocine
Phenylpiperidines	Fentanyl Meperidine Remifentanil Sufentanil
Phenylpropylamines	Tapentadol Tramadol
Diphenylheptanes	Methadone
Source: [27]	*Table 2*

Opioid-Induced Hyperalgesia

Opioid-induced hyperalgesia is defined as "a state of nociceptive sensitization caused by exposure to opioids" [24]. Patients with opioid-induced hyperalgesia experience a sensitivity to pain that could be the same as their original, underlying pain or could originate from a different source [25]. Opioid-induced hyperalgesia can present in a way that is often mistaken for opioid tolerance. Tolerance to the analgesic effects of opioids can develop and requires escalating doses of opioids to maintain the same level of pain control. If a patient has tolerance to an opioid, pain will decrease when the opioid dose is increased. If the patient has opioid-induced hyperalgesia, increasing the opioid makes the pain even worse and a decrease in the opioid dose relieves the pain [24]. Switching opioids can also help relieve hyperalgesia [26]. Opioid-induced hyperalgesia should be considered in the differential diagnosis when opioid therapy fails [25].

Opioid Allergy

Opioid allergy is a common patient complaint. However, less than 2% of opioid reactions are "true allergies" and may be more appropriately categorized as pseudoallergies. A pseudoallergy is a side effect of opioids that can resemble an allergy but is usually caused by histamine release from mast cells. Symptoms of a pseudoallergy often include flushing, itching, rash, or hives. Opioids most associated with pseudoallergies include codeine, morphine, and meperidine. True allergies are more likely with symptoms such as severe hypotension; breathing, speaking, or swallowing difficulties; or swelling

of the face, lips, mouth, tongue, pharynx, or larynx. Patients allergic to one opioid are thought to be less likely to react to an opioid in a different structural class (***Table 2***). Because true allergy is rare, there is not enough information to assess the chance of cross-reactivity. In addition, several opioids' product labeling contraindicates their use in patients with true allergies to any opioid.

Opioid Stewardship Considerations

Long-term opioid use, which is associated with the development of opioid use disorder, overdose, and other risks, often begins with opioid use for acute pain [28]. Clinicians and facilities should take steps to ensure prescribers and patients are on the same page regarding opioid risks and benefits. For example, before surgery, educate patients about postoperative pain. Tolerable pain and improved function are goals; complete pain relief is not always realistic. Organizational strategies to reduce unnecessary or unsafe opioid prescribing include [28]:

- Avoid storing long-acting opioids in acute pain areas.
- Remove long-acting opioids from preoperative order sets.
- Have opioid orders default to starting doses.

Opioid safety is also a consideration at transitions of care. Patients taking medications for opioid dependence should be identified on admission, as there are special considerations for managing acute pain in these patients. Inpatient opioid use should be reviewed to help assess the need for a discharge opioid prescription. In all cases, caution should be exercised when switching patients between opioids to ensure equianalgesic doses are properly considered [28].

SEDATION IN ADULT ICU PATIENTS

WHEN IS SEDATION NEEDED IN CRITICALLY ILL PATIENTS?

Sedation should only be considered after a patient's pain is adequately controlled. The analgesia-based sedation model (also called analgosedation or analgesia-first sedation) first addresses pain and discomfort, then adds sedative agents if necessary. Analgesia-first sedation is suggested in treatment guidelines for adult ICU patients [3]. The advantages of analgesia-based sedation include a reduced need for sedatives, shorter duration of mechanical ventilation, and shorter duration of ICU stay. Disadvantages of analgesia-based sedation may include an increased risk of delirium. However, sedation titration (e.g., titrating to awake yet calm according to the Richmond Agitation-Sedation Scale [RASS]) can be used to minimize this risk [29].

Heavy or deep sedation, once much more common in ICUs, is now often referred to as oversedation. Deep sedation has been associated with increased morbidity and mortality, and more recent sedation protocols for patients in the ICU emphasize the importance of analgesia-based sedation; early mobility and physical therapy; spontaneous awakening and breathing trials, and the use of the enteral route, when appropriate [2]. The goals of light sedation (as opposed to deep sedation) are to keep a patient able to tolerate mechanical ventilation and other procedures required for care, calm and comfortable, and easily arousable [2].

Inappropriate levels of sedation (too high or too low) are not uncommon in patients in the ICU [7]. It is important to assess a patient's level of sedation by using objective assessment tools. In one study, nurses found 32% of patients to be oversedated using objective measures, while only 3% were considered oversedated by subjective measures [7]. As such, the use of scales (e.g., RASS, Riker Sedation-Agitation Scale [SAS], Motor Activity Assessment Scale [MAAS]) is preferred for objectively measuring quality and depth of sedation in adult ICU patients [3; 6]. These scales assess where a patient lies on a continuum between "combative" or "dangerously agitated" and "unarousable." Appropriate use of these scales can lead to lower doses of sedative agents and reduced duration of mechanical ventilation [3]. The RASS rates patients based on behavior, verbal stimulation, and physical stimulation. Scores range from +4 (indicating combative, violent, immediate danger to staff) to -5 (for patients who are unarousable, with no response to verbal or physical stimulation). The Riker SAS assesses level of sedation based on behavior, verbal stimuli, and physical stimuli. The scale ranges from 7 (dangerous agitation) to 1 (unarousable).

Appropriate levels of sedation will vary based on patient specific situations. For example, light sedation is not appropriate for patients receiving neuromuscular blocking agents. In these patients, ensure that analgesics and sedatives are titrated to deep sedation before starting a neuromuscular blocker. If patients are paralyzed with neuromuscular blocking agents, an objective measure of brain function, such as the bispectral index monitor (BIS), a quantitative electroencephalograph (EEG) to assess the depth of anesthesia, could be used to assess sedation status [3]. Deeper sedation may also be needed in patients with severe respiratory distress in order to ensure optimal ventilation (i.e., ventilator synchrony).

The Society of Critical Care Medicine suggest using light sedation (versus deep sedation) in critically ill, mechanically ventilated adults.

(https://www.sccm.org/Clinical-Resources/Guidelines/Guidelines/Guidelines-for-the-Prevention-and-Management-of-Pa. Last accessed January 25, 2024.)

Level of Evidence: Low

COMPARISON OF COMMONLY USED NON-BENZODIAZEPINE SEDATIVES		
Properties	**Propofol**	**Dexmedetomidine**
Mechanism	GABA agonist	Alpha-2 receptor agonist
Onset	1 to 2 minutes	5 to 10 minutes
Common side effects	Bradycardia Hypotension Respiratory depression Neuroexcitatory effects Pancreatitis Hypertriglyceridemia	Bradycardia Hypotension
Comments	Use for more than 48 hours can lead to a prolonged duration of action Anticonvulsant effects, but no analgesic effects	Analgesic effects, but no anticonvulsant effects Ideal for non-mechanically ventilated patients as it lacks respiratory depression effects Not appropriate for use in patients requiring deep sedation (e.g., mechanically ventilated patients)
Source: [2; 3; 6; 7; 9; 33; 36]		*Table 3*

To reduce drug accumulation and oversedation, the following strategies may be helpful:

- Daily sedation interruption
- Giving a bolus before increasing the infusion rate
- If using benzodiazepines, giving intermittent bolus doses of benzodiazepines instead of continuous infusions
- Use of integrated sedation protocols
- Use of agents with ultra-short half-lives

Daily interruption of sedation or targeting a light level of sedation is a conditional recommendation in the pain and sedation treatment guidelines for mechanically ventilated ICU patients, due to the low quality of evidence available [3]. Daily interruption of sedation in mechanically ventilated ICU patients has been shown to reduce mortality, duration of stay, and the risk of adverse events [5; 30]. However, this strategy is often not used or optimized in these patients [5; 31].

Daily sedation interruption, defined as short-term discontinuation of IV sedatives and sometimes analgesics, and nursing-protocolized-targeted sedation are both options to achieve and maintain appropriate light sedation (but are not appropriate for patients requiring deep sedation due to use of neuromuscular blocking agents) [3]. Goals include limiting drug accumulation, promoting wakefulness, allowing for neurological assessments, increasing tolerance for drug discontinuation, and preparing patients for extubation [31]. The medications are adjusted or stopped, then the patient is observed until they are awake, uncomfortable, or agitated. If the patient is awake and comfortable, sedative infusions are not recommended to be restarted. However, if the patient is agitated or uncomfortable, medications are restarted, typically at 50% of the previous dose and titrated to desired sedation score [32]. Both options are considered safe ways to assess and maintain appropriate light sedation [3].

DRUGS OF CHOICE FOR SEDATION IN CRITICALLY ILL PATIENTS

What are potential complications of oversedation in the ICU?

Experts point out qualities of the ideal sedative medication: inexpensive, minimal risk of respiratory depression, elimination independent of kidney or liver function, short half-life, and no active metabolites. However, no currently available agent meets all these criteria [6].

Sedative agents commonly used in the adult ICU setting include propofol, dexmedetomidine, ketamine, and benzodiazepines (e.g., lorazepam, midazolam) (***Table 3***) [3; 6]. Some critically ill patients receive propofol plus additional agents for sedation; however, as discussed, there is a trend toward the use of lighter sedation [7]. Note that this parallels the trend to keep patients comfortable while awake, interactive, and oriented.

Potential consequences of undersedation include [7]:

- Hypoxemia
- Increased stress
- Severe anxiety and/or agitation
- Unplanned extubation

Conversely, potential consequences of oversedation are [7]:

- Cognitive impairment
- Depressed respiratory drive
- Increased duration of ICU stays
- Increased duration of mechanical ventilation
- Increased risk of infection

Propofol

Propofol is an anesthetic and gamma-aminobutyric acid (GABA) agonist [6; 7]. It has sedative, hypnotic, anxiolytic, amnestic, antiemetic, and anticonvulsant properties; it does not have analgesic properties [2; 3]. Its amnestic properties are less than with benzodiazepines in adult ICU patients at light levels of sedation [9]. Propofol has a rapid onset of action (one to two minutes) and a short duration (as short as three minutes with short-term use) [6; 9]. This is an advantage for rapid sedation as well as rapid awakening [7]. However, long-term administration of propofol (more than 48 hours) can lead to a prolonged duration of action [9].

Propofol is given as a continuous infusion, not by intermittent dosing, due to its short half-life and dose-dependent hypotension. It is metabolized mainly in the liver to inactive metabolites that are excreted in urine [18].

Side effects of propofol include hypotension (occurring in up to 25% of patients), bradycardia, respiratory depression, neuroexcitatory effects, pancreatitis, and hypertriglyceridemia [2; 6; 7]. Propofol is supplied as a lipid emulsion. Triglycerides should be monitored in patients at risk for hypertriglyceridemia and during prolonged therapy. In addition, calories from propofol should be counted toward a patient's caloric goals [2]. The 10% lipid emulsion of many propofol formulations has approximately 1.1 kcal (0.1 g of fat) per mL of propofol [32].

It is important to be careful about look-alike errors with propofol. Propofol has a similar milky-white appearance to liposomal bupivacaine or clevidipine.

The inactive ingredients in these emulsion formulations can vary and may affect their appropriateness for different patients. For example, the emulsion formulations contain soybean oil and egg lecithin. Other formulations contain sulfites or benzyl alcohol. These are all ingredients that may cause allergic reactions in some patients [18].

High doses of propofol (more than 65–80 mcg/kg/minute) as well as prolonged infusions (more than 48 hours) are associated with propofol-related infusion syndrome (PRIS) [34]. This is a serious side effect that may involve arrhythmias, hypotension, hypertriglyceridemia, kidney dysfunction, severe metabolic acidosis, and rhabdomyolysis [7; 9]. The incidence of propofol infusion syndrome is about 1% and mortality is up to 33% [9]. The minimally effective dose of propofol should always be used. Monitoring should include serum creatine kinase, serum triglycerides, and observation for any unexplained anion gap metabolic acidosis. Supportive care, including early recognition and prompt discontinuation of propofol, is essential, as there are no effective treatments available for propofol infusion syndrome [6].

Some patients may require higher sedative doses than expected even to achieve light sedation, such as those with COVID-19. There are no hard and fast rules when treating these patients, but certain strategies should be considered to ensure safe and appropriate use [3; 21; 33; 34]. Generally, use propofol first. All patients should be monitored for hypotension and symptoms of the rare but fatal PRIS, unexplained metabolic acidosis, rhabdomyolysis, and bradycardia. There is no consensus on a maximum propofol dose, but PRIS risk goes up with higher doses and longer durations. Clinicians should consider allowing short-term use above the standard, such as up to 80 mcg/kg/min for a few days. With higher doses, triglycerides should be checked more frequently (e.g., a few times per week). Propofol is often stopped for triglyceride levels greater than 500 mg/dL, but a higher threshold should be considered, because pancreatitis is rare when triglyceride levels are less than 1,000 mg/dL. If giving high propofol doses for multiple days, other sedatives may be added; using lower doses of each medication may limit side effects.

Alternatives should be available when propofol is not an option due to issues such as shortages. Dexmedetomidine may be considered for light sedation. Patients administered dexmedetomidine should be monitored for bradycardia and hypotension. This agent does not provide deep-enough sedation to use with a paralytic. If deep sedation is needed, add or switch to a midazolam drip. It is important to limit use of midazolam when able, because benzodiazepines are linked to delirium risk. A ketamine drip may be considered as an add-on option, especially with hypotensive patients, because it can raise blood pressure, and those requiring additional analgesia. Ketamine use should be avoided in patients with decompensated heart failure, and all patients should be monitored for tachycardia and increased secretions.

Dexmedetomidine

Dexmedetomidine is a relatively selective, alpha-2 receptor agonist [35]. It has analgesic, anxiolytic, sedative, and opioid-sparing properties. Dexmedetomidine has no anticonvulsant activity and should never be used alone in alcohol withdrawal [2]. It can be used for sedation in non-mechanically ventilated patients due to its lack of significant respiratory depression [3; 6; 7]. Patients are easily arousable with dexmedetomidine but can remain sedated when undisturbed [2]. The use of dexmedetomidine is associated with reduced duration of mechanical ventilation and possibly a lower incidence of delirium in comparison with benzodiazepines [3; 7].

Dexmedetomidine has an onset of action of 5 to 10 minutes, a peak effect at about 1 hour, and a short duration of action (with a half-life of 2 to 3 hours). It is administered as a continuous infusion, rarely with a bolus dose [3].

COMPARISON OF OPIOIDS COMMONLY USED IN CRITICALLY ILL PATIENTS			
Characteristics	**Lorazepam**	**Midazolam**	**Diazepam**
Onset	15 to 20 minutes	2 to 5 minutes	2 to 5 minutes
Duration of effect[a]	6 to 8 hours	30 to 60 min	2 to 4 hours
Frequency	Intermittent or continuous	Intermittent or continuous	Only intermittent
Drug interactions	Low risk	Metabolized by CYP3A4	Metabolized by CYP2C19 and 3A4
Active metabolites	No	Yes	Yes
Dose adjustment	Not if mild or moderate kidney or liver impairment	Kidney, liver	Kidney, liver
Administration	Contains propylene glycol IV incompatibilities Risk of precipitation	No propylene glycol	Contains propylene glycol
Risks	Delirium Can accumulate in peripheral tissues	Delirium	Delirium Injection site pain and phlebitis
[a]When used intermittently for less than 48 hours			
Source: [2; 38]			*Table 4*

Bradycardia and hypotension are common side effects with continuous infusions of dexmedetomidine [6]. Hypotension can be significant and adverse effects are not always quickly reversed when the infusion is stopped. Hypertension can occur after the infusion is stopped and with bolus injections. The rapid administration of a bolus dose can cause cardiovascular instability, tachycardia, bradycardia, or heart block. For this reason, the initial bolus may be avoided in most patients [6; 7].

Dexmedetomidine is metabolized in the liver. Lower doses should be used initially in patients with severe liver disease and titrated to effect [36]. Product labeling of dexmedetomidine warns of tolerance, tachyphylaxis, and increased adverse effects when used for more than 24 hours' duration [36]. However, several studies have shown safety and efficacy with longer durations [9].

Benzodiazepines

Historically, benzodiazepines have been the most commonly used agents for sedation in the ICU setting [2]. However, guidelines now recommend benzodiazepines as second-line therapy, with dexmedetomidine, propofol, and analgesia-based sedation regimens being preferred [3; 6]. Benzodiazepines seem to be associated with poorer patient outcomes, such as development of delirium, longer duration of mechanical ventilation, and longer duration of ICU stay in medical, surgical, trauma, and burn patients [2; 6; 7]. Still, the use of benzodiazepines remains important in critically ill patients for treatment of seizures and alcohol withdrawal. They also have a role in deep sedation (when indicated) or to reduce doses of other sedatives [3].

Benzodiazepines have anxiolytic, amnestic, sedative, hypnotic, and anticonvulsant effects, but no analgesic activity (***Table 4***) [3]. Adverse effects include respiratory depression and hypotension. These effects are more pronounced with concomitant cardiopulmonary depressants, especially opioids [3].

Lorazepam and midazolam are commonly used in the ICU setting [6]. They are given either by intermittent or, less commonly, by continuous infusion. Diazepam is also used occasionally and is given by intermittent infusions, not continuously [9]. Diazepam and midazolam have a quicker onset of action (2 to 5 minutes) than lorazepam (15 to 20 minutes).

Repeated dosing of benzodiazepines causes accumulation in adipose tissue [36]. This accumulation increases the duration of effect after they are stopped, particularly in obese patients. Both diazepam and midazolam are metabolized by the liver to active metabolites [2; 6]. These active metabolites are eliminated via the kidneys, so the effects of diazepam and midazolam may be prolonged in patients with impaired kidney function [2; 6; 7]. Lorazepam is metabolized by the liver but does not have active metabolites [6]. Diazepam can cause phlebitis when injected into peripheral veins [9].

Note that injectable lorazepam and diazepam are formulated with a propylene glycol solvent, and some patients have allergies to this solvent. There have also been reports of toxicity (e.g., metabolic acidosis, hypotension) with higher-than-recommended doses of lorazepam. Patients with kidney impairment or using high doses of lorazepam (1 mg/kg/day or more) for prolonged periods of time may be at increased risk of toxicity [2; 37].

Neuromuscular Blockers

Neuromuscular blocking agents (e.g., atracurium, vecuronium, cisatracurium) paralyze skeletal muscles but do not have sedative or analgesic properties. The use of paralysis via neuromuscular blockers in mechanically ventilated adult ICU patients has decreased considerably due to the potential for worse patient outcomes with this deep sedation. Within the ICU, neuromuscular blockade is still useful in certain mechanically ventilated patients, such as to facilitate breathing synchronization, to reduce the severity of muscle spasms associated with tetanus, and to decrease oxygen consumption [6; 38; 39].

In the ICU, the most commonly used neuromuscular blockers are succinylcholine and rocuronium, with rocuronium considered the preferred agent, particularly for rapid sequence intubation [57]. Rocuronium is the most recently developed neuromuscular blocking agent, introduced in 1992, and developed as a short- to intermediate-acting nondepolarizing agent with an extremely rapid, dose-based onset [64; 65; 66]. The usual intubating dose is 0.6–1.2 mg/kg. Its rapid onset (45 to 90 seconds) has placed it as a nondepolarizing alternative to succinylcholine; however, doses sufficient to speed onset to this degree come with long durations of action (60 to 90 minutes). In the patient whose airway is difficult and in whom the chance of failure to rapidly intubate may lead to a comorbid or mortal event, succinylcholine has been the criterion standard. This circumstance, however, has changed with the introduction of sugammadex to clinical practice in the United States. This novel reversal agent works by surrounding the molecules of rocuronium, precluding it from binding to the nicotinic acetylcholine receptor [67]. Following an intubating dose of rocuronium, administration of sugammadex allows the complete recovery of neuromuscular function in a shorter time than an equipotent dose of succinylcholine.

Succinylcholine is an older agent, but it is still used in some facilities. Upon injection, succinylcholine rapidly distributes throughout the body, binding to the acetylcholine receptors on the postsynaptic muscle tissue. Instead of preventing muscular contraction, it causes a random and uncoordinated firing of these receptors, resulting in the physical manifestation of anything from minor twitching to tonic contraction of major muscle groups. These fasciculations are an indicator that the drug is working. After the muscle groups tighten, they relax, but the presence of the drug on the receptors does not allow the muscle tissue to immediately repolarize [65].The effective dose is 0.5–0.6 mg/kg, and the usual intubating dose is 1.0–1.5 mg/kg. Doses in excess of 5 mg/kg are associated with a phase II block, which unpredictably prolongs the action of succinylcholine. The onset of action is 1 minute, with a return to normal typically seen after 9 to 13 minutes.

Atracurium and cisatracurium are generally the preferred agents in patients with kidney or liver impairment, patients receiving systemic corticosteroids, and patients with acute respiratory distress syndrome, targeted temperature management, or traumatic brain injury [6; 40]. Both undergo Hoffman elimination (independent of the liver or kidneys) to inactive metabolites. When neuromuscular blockade is used in mechanically ventilated ICU patients, attempts should be made to limit drug dose as well as duration of use [2].

Neuromuscular blockers are considered high-alert medications. It is important to develop and follow preparation and administration policies to ensure safety (e.g., application of auxiliary labels to IV bags, pharmacy and nursing double checks, specific placement on delivery to patient care units). Other ways to focus on safe use of neuromuscular blocking agents are to ensure the lowest doses for the shortest duration to minimize complications, such as myopathy, and to use clinical endpoints (e.g., ventilator synchrony) and train-of-four to monitor. Auxiliary medications (e.g., eye lubricants, venous thromboembolism prophylaxis) are necessary in many patients.

While mechanical ventilation is possible without the coadministration of neuromuscular blocking drugs, some forms of mechanical ventilation will be difficult for the patient to tolerate. For example, as the mechanical ventilator inflates the lungs, a volume will be reached that triggers the Hering-Breuer response [68]. This reflex ordinarily stops negative pressure inspiration in the normally breathing adult; however, in the mechanically ventilated patient, it may cause the patient to violently attempt to cough, more commonly known as "bucking" on the ventilator. This phenomenon may be attenuated by either sedation or narcotic analgesia, but the doses of such medications may result in prolonged inhibition of normal respiration and delay extubation. Further, in patients with either acute lung injury or acute respiratory distress syndrome (sometimes referred to as noncardiogenic pulmonary edema), the administration of neuromuscular blockade can decrease oxygen consumption [69]. In one study of 340 patients requiring mechanical ventilation secondary to acute respiratory distress syndrome, a group that received a 15-mg bolus dose of cisatracurium followed by an infusion of 37.5 mg/hour for 48 hours resulted in a 90-day mortality rate of 31.6%, compared with a mortality rate of 40.7% in those not receiving the protocol [70]. While the importance of the judicious use of neuromuscular blockers in the critically ill cannot be understated, one study provides clear and convincing evidence of the importance of a sufficient level of sedation that should also be given to these patients. In their study, patients were more likely to develop delirium in the absence of or inadequacy of sedation [71]. In their research, 64.4% of mechanically ventilated patients experienced delirium and had a 30-day mortality rate of 30.3%, compared with a rate of 11.9% in those not experiencing delirium [71]. Clinicians should always keep in mind the concept that neuromuscular blockers offer no diminution of central nervous system function whatsoever, and there can be few things as terrifying as being paralyzed and wide awake.

With the use of a peripheral nerve stimulator and the co-administration of sedation, the ICU staff can closely monitor a patient's degree of neuromuscular blockade [72]. Patients requiring prolonged neuromuscular blockade in the ICU are best treated with intravenous infusions of intermediate-acting agents. As with all hospitalized patients, the goal is to treat the underlying disease or injury as quickly as possible, and then wean the patient from the ventilator in a quick and efficient manner. While intermittent boluses of neuromuscular blockers will prevent patient movement, they may impede the reversal and weaning process. A large loading dose of neuromuscular blocking drug, given to ensure quick onset, has the disadvantage of exceeding the therapeutic dose levels and extinguishing the train-of-four response (no twitches). Until the dose begins to degrade, there is no way to determine the extent of neuromuscular blockade. Indeed, there may be a supramaximal dose, resulting in prolonged blockade. The infusion dose, though taking a bit longer to set up, stops at the desired point. The lack of peaks and nadirs ensures the correct dose throughout the administration of the drug, easing recovery from neuromuscular blockade.

Finally, the administration of large bolus doses of neuromuscular blocking agents in the ICU has been associated with prolonged blockade [72]. This is attributed primarily to those agents degraded by the liver and eliminated by the kidney. During the peak stages of the patient's illness or injury, hepatic and/or renal function may decrease. Agents such as pancuronium and vecuronium, with significant hepatic breakdown, active metabolites, and diminished renal excretion, have been associated with prolonged neuromuscular blockade lasting days or weeks after the cessation of administration [72]. This phenomenon appears especially linked to those patients presenting with sepsis. One group of researchers speculated the aggravating effects of neuromuscular blockers in these patients may also be due to degraded renal function [73].

WITHDRAWAL OF THERAPY

Which characteristic may increase a patient's risk for withdrawal from analgesics and sedatives in the ICU?

Withdrawal from analgesics and sedatives is linked to longer time on the ventilator and in the ICU. Several strategies have been identified to help prevent withdrawal when stopping high doses of ICU analgesics and sedatives, including identifying patients at risk for withdrawal, such as:

- Patients receiving five more days of analgesics and sedatives
- Patients receiving high doses
- Younger patients
- Obese patients
- Patients with a history of chronic opioid, alcohol, or benzodiazepine use

Taking proactive steps to minimize withdrawal is also recommended. This involves weaning doses, instead of stopping abruptly, and using a multimodal approach to sedation and analgesia. Safely tapering agents may consist of reducing opioid or benzodiazepine infusion by 10% to 30% each day or reducing the opioid infusion by 20% to 40% initially, with additional reductions of 10% every 12 to 24 hours. Alternatively, patients may be switched to an oral substitute, with the infusion tapered by 10% to 30% with each oral dose, then taper oral agent by 10% to 30% each day once stable off infusion. If a more conservative oral dose is started, a slower infusion taper may be needed. The tapering plan should be clearly communicated at transitions of care to minimize the risk of patients ending up on unneeded opioids or benzodiazepines long-term.

DELIRIUM IN ICU PATIENTS: PREVENTION AND TREATMENT

Which strategies may help decrease the risk of delirium in ICU patients?

Delirium is an acute change in mental status characterized by inattention and disorganized thinking or altered level of consciousness [6; 9]. Up to 8 out of 10 mechanically ventilated ICU patients may have delirium, but it can occur whether a patient is mechanically ventilated or not [6; 9].

General risk factors for delirium are [41; 42; 43; 44]:

- Age older than 65 years
- Alcohol misuse
- Cognitive impairment or dementia
- Depression
- Poor vision or hearing
- Poor functional status
- Post-surgery
- Severe or critical illness

Risk factors with the strongest association for the development of delirium in ICU patients are [3]:

- Advanced age
- Benzodiazepine use
- Blood transfusion
- History of coma
- More severe illness
- Pre-existing dementia

Patients with delirium have an impaired ability to receive, process, and store information [2]. These patients may be hyperactive and are often described as combative or agitated, with delusions, hallucinations, and psychomotor agitation; others will be hypoactive, with depression, confusion, decreased mental activity, and withdrawal [2; 9].

In general, symptoms of delirium are [9]:

- Change in cognition such as memory deficit, disorientation, or language disturbance, or a perceptual disturbance (such as hallucinations or delusions)
- Reduced ability to focus, sustain, or shift attention
- Reduced clarity of awareness of the environment

Other common symptoms may include [9]:

- Abnormal psychomotor activity
- Emotional disturbances such as fear, anxiety, anger, depression, apathy, or euphoria
- Sleep disturbances

The onset of symptoms is typically acute (i.e., over one to two days). Delirium has been described as "acute brain failure." The course of symptoms is typically fluctuating.

Delirium in ICU patients is associated with long-term cognitive impairment, increased mortality, increased duration of mechanical ventilation, and increased duration of ICU and hospital stay [2; 3; 7]. The cause of delirium is not clear, although it has been associated with the use of sedative medications, such as benzodiazepines, and patient factors, such as cognitive impairment, sleep deprivation, immobility, visual and hearing impairment, and dehydration [2; 6]. Oversedation and undersedation are also risk factors for the development of delirium [45]. Strategies to reduce these factors, which may help decrease the risk of delirium, include [2]:

- Early mobilization (strongly recommended)
- Regulation of sleep-wake cycles
- Creating an environment conducive to uninterrupted sleep (e.g., clustering patient care activities such as bathing and lab tests)
- Provision of eyeglasses and hearing aids
- Noise reduction
- Controlling light to mimic a normal day and night schedule

In some cases, delirium may also be disease-induced (e.g., severe sepsis). In these cases, treatment of the underlying cause can reduce the incidence, severity, and duration of delirium. Delirium is also associated with drug or alcohol withdrawal after abrupt discontinuation, typically manifesting as hyperactive delirium [3].

When present, clinicians should work to ensure that the underlying causes of delirium are addressed. This assessment is guided by the mnemonic THINK:

- T: Toxic situations (e.g., medications, dehydration, organ failure), or use tight titration of medications that can cause delirium (i.e., use low doses)
- H: Hypoxemia
- I: Infection or immobilization
- N: Nonpharmacologic interventions (e.g., hearing aids, glasses, orientation, environment conducive to sleep)
- K: K+ (potassium) or other electrolyte problems

In addition, withdrawal of alcohol, tobacco, or benzodiazepines should be considered as a potential cause. The patient's home medications list should be reviewed to identify less well-known potential causes of withdrawal delirium. For example, there are published case reports of delirium in patients withdrawn from selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), baclofen, gabapentin, pregabalin, and antipsychotics [61; 62; 63].

Validated assessment tools, such as the Confusion Assessment Method for ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC), can be used to detect delirium in adult ICU patients [2; 3]. The CAM-ICU requires patient interaction and results in either a positive or negative outcomes; the target is negative. The ICDSC also relies on patient interaction. It is scored on a range from 0 to 8, with a score of 3 of greater indicating delirium.

According to the Society of Critical Care Medicine, critically ill adults should be regularly assessed for delirium using a valid tool.

(https://www.sccm.org/Clinical-Resources/Guidelines/Guidelines/Guidelines-for-the-Prevention-and-Management-of-Pa. Last accessed January 25, 2024.)

Level of Evidence: Ungraded

Medications should be reviewed and recommendations made to reduce the risk of delirium. The total number of medications should be reduced, with a particular focus on minimizing the use of anticholinergics (e.g., diphenhydramine, promethazine), benzodiazepines, and opioids (especially meperidine) [44; 46; 47]. If possible, the doses of medications that could cause delirium should be reduced, and use of psychoactive medications in general should be minimized [48; 50]. If feasible, administration schedules should be modified to maintain a normal sleep-wake cycle [43]. Any sedatives used should have a specific indication, targeting a light level of sedation [3].

Pharmacologic prevention of delirium is not recommended [3]. The potential benefit of cholinesterase inhibitors (e.g., rivastigmine, donepezil), antipsychotics, gabapentin, and melatonin have all been studied, but there is no consistent evidence to support their use.

Further, clinicians should refrain from routinely using medications to treat delirium, as high-quality evidence to support medications to treat delirium is generally lacking [3]. The first step is to address the underlying cause when possible, as discussed. Antipsychotics should be reserved for treatment of severe distress (e.g., due to hallucinations or delusions) or for agitated patients that may pose a risk of harm to self or others despite nondrug interventions [3; 45; 49].

If use of an antipsychotic is necessary, start with a low dose and titrate to symptom control [43; 50]. For example, haloperidol may be administered at a dosage of 1–5 mg IV every 12 hours, as needed, with consideration to reducing starting dose by 50% in older adult patients [51]. IV haloperidol can be given every four to eight hours if needed, but the total daily dose should not exceed 20 mg. Because of the age-related, gradual decline in glomerular filtration rate, patients older than 50 years of age may have a lower renal clearance and longer elimination half-life of haloperidol; caution is therefore required when using haloperidol for treatment of acute delirium in elderly patients and others with reduced renal and hepatic function [50]. Elderly patients are also more susceptible to extrapyramidal side effects of haloperidol, such as acute dystonia, parkinsonism, or tardive dyskinesia, each of which may impair the ability to swallow and increase the risk for aspiration pneumonia.

Patients who are being administered antipsychotics should be monitored for QT prolongation. It seems rare when using low antipsychotic doses, but a 12-lead electrocardiogram (ECG) may be indicated to monitor high-risk patients, such as those with a baseline QT greater than 450 ms in men or 460 ms in women, or those taking amiodarone or other medications likely to prolong QT. Generally, the antipsychotic should be halted if the QT rises more than 60 ms from baseline or to greater than 500 ms [52; 53].

Best practice is to consider discontinuing antipsychotics when patients are transferred to the floor if at all possible. An estimated one in five patients receiving an antipsychotic for the first time in the hospital will be discharged with a likely unnecessary prescription [54].

CONSIDERATIONS FOR CULTURALLY AND LINGUISTICALLY COMPETENT CARE

The assessment of agitation, sedation, and delirium in the ICU is dependent on evaluation of the patient's responses to screenings and/or stimuli. In addition, patient and family education can be essential to ensuring optimal patient-centered care.

A study of culturally competent care among physicians and nurses in Australian ICUs found that deficits in the consideration and documentation of cultural sensitive care, particularly end-of-life care [58]. The author presented three recommendations to improve care for critically ill patients [58]:

- Comprehensive documentation is required of how clinicians assess patient and family member cultural wishes and preferences, in conjunction with how clinicians attempt to address these cultural needs. It is recommended that social care, inclusive of cultural needs, is also routinely documented.
- It is recommended that social workers are more routinely involved in patient care commencing from admission to the ICU. The roles and expectations of clinicians and social workers in assessing and documenting cultural wishes and preferences should be acknowledged by the whole healthcare team and documented in the policies and procedures to reduce the risk of omission and role ambiguity.
- Clinicians should aim to use interpreters in all family meetings in which language barriers exist to reduce potential conflict and enhance communication.

Depending upon the patient's language, an interpreter may be difficult to locate. Or, an organization may not have the funds to bring in an interpreter. Also, bringing in an interpreter creates a triangular relationship with a host of communication dynamics that must be negotiated [74]. Many view interpreters merely as neutral individuals who communicate information back and forth. However, another perspective is that the interpreter is an active agent, negotiating between two cultures and assisting in promoting culturally competent communication and practice [75; 76]. In this more active role, the interpreter's behavior is also influenced by a host of cultural variables such as gender, class, religion, educational differences, and power/authority perceptions of the patient [75; 76]. Consequently, an intricate, triangular relationship develops between all three parties. Another factor affecting the communication process is the fact that many interpreters are not adequately trained in the art of interpretation in mental health and general health settings, as there are many technical and unfamiliar terms. An ideal interpreter goes beyond being merely proficient in the needed language/dialect [77]. Interpreters who are professionally trained have covered aspects of ethics, impartiality, accuracy, and completeness [78]. They are also well-versed in

interpreting both the overt and latent content of information without changing any meanings and without interjecting their own biases and opinions [78]. Furthermore, knowledge about cross-cultural communication and all the subtle nuances of the dynamics of communicating in a mental health or general health setting is vital [76; 77].

On the patients' side, they may be wary about utilizing interpreters for a host of reasons. They may find it difficult to express themselves through an interpreter [79]. If an interpreter is from the same community as the patient, the patient may have concerns about sharing private information with an individual who is known in the community and the extent to which the information disclosed would remain confidential. In some cases, raising the issue of obtaining an interpreter causes the patient to feel insulted that their language proficiency has been questioned. Finally, if an interpreter is from a conflicting ethnic group, the patient may refuse having interpreter services [74]. The ideal situation is to have a well-trained interpreter who is familiar with health and mental health concepts.

If an interpreter is required, the practitioner must acknowledge that an interpreter is more than a body serving as a vehicle to transmit information verbatim from one party to another [79]. Instead, the interpreter should be regarded as part of a collaborative team, bringing to the table a specific set of skills and expertise [79]. Several important guidelines should be adhered to in order to foster a beneficial working relationship and a positive atmosphere.

A briefing time between the practitioner and interpreter held prior to the meeting with the patient is crucial. The interpreter should understand the goal of the session, issues that will be discussed, specific terminology that may be used to allow for advance preparation, preferred translation formats, and sensitive topics that might arise [77; 79; 80]. It is important for the patient, interpreter, and practitioner to be seated in such a way that the practitioner can see both the interpreter and patient. Some experts recommend that the interpreter sit next to the patient, both parties facing the practitioner [78].

The practitioner should always address the patient directly. For example, the practitioner should query the patient, "How do you feel?" versus asking the interpreter, "How does she feel?" [78]. The practitioner should also always refer to the patient as "Mr./Mrs. D" rather than "he" or "she" [79]. This avoids objectifying the patient.

At the start of the session, the practitioner should clearly identify his/her role and the interpreter's role [79]. This will prevent the patient from developing a primary relationship or alliance with the interpreter, turning to the interpreter as the one who sets the intervention [77]. The practitioner should also be attuned to the age, gender, class, and/or ethnic differences between the patient and the interpreter [79]. For example, if the patient is an older Asian male immigrant and the interpreter is a young, Asian female, the practitioner must be sensitive to whether the patient is uncomfortable given the fact he may be more accustomed to patriarchal authority structures. At the conclusion of the session, it is advisable to have a debriefing time between the practitioner and the interpreter to review the session [77; 79; 80].

In this multicultural landscape, interpreters are 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 diagnostic procedures, treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered.

CONCLUSION

Optimizing the management of analgesia, sedation, and delirium in adult ICU patients is important for improving outcomes, such as the duration of mechanical ventilation and the duration of ICU stay. Using validated tools to detect and monitor a patient's level of pain and sedation should be part of the treatment plan. There are several agents that can be used to achieve analgesia and sedation, and having a familiarity with their properties, benefits, and risks can help ensure the best therapy is given for each patient.

Customer Information/Evaluation insert located between pages 48–49.

Herbal Medications: An Evidence-Based Review

Includes 10 Pharmacotherapeutic/Pharmacology Hours

Audience

This course is primarily designed for nurses, physicians, and pharmacists. However, considering the widespread availability and increased use of herbal medications, other healthcare professionals, including social workers and clinical therapists, will also benefit from this course.

Course Objective

Considering the pharmacologic interactions between herbal medications (HMs) and conventional medications, it is paramount to increase the awareness and knowledge of healthcare professionals about HMs. The purpose of this course is to increase healthcare professionals' awareness of the potential risks and benefits of HMs from an evidence-based perspective and promote the planned inclusion of HM use in patients' medical history. This course should allow healthcare professionals to discuss HMs in a knowledgeable and succinct manner with patients and colleagues.

Learning Objectives

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

1. Discuss the prevalent current and historical use of HMs in North America.
2. Explain the need to inquire about the use of HMs during preparation of a patient's medical history, including components of a culturally sensitive assessment.
3. Discuss the pharmacology (i.e., pharmacokinetics, pharmacodynamics, drug interactions, adverse drug reactions, toxicology) of HMs.
4. Describe the differences between the process of development and approval of HMs versus conventional medications, and the implications of health claims and therapeutic efficacy of HMs.
5. Outline the merits and limitations associated with the application of contemporary scientific principles and methodologies (i.e., evidence-based medicine) to assess the efficacy and safety of HMs.
6. Discuss, based on scientific and conventional medical principles, the pharmacologic properties, efficacy, safety, toxicology, therapeutic indications, and recommended dosages of saw palmetto and St. John's wort.
7. Describe the potential risks and benefits of ginkgo.
8. Identify key characteristics of ginseng.
9. Discuss the use of echinacea and kava, including potential adverse effects.
10. Review the use of garlic and valerian as HMs.
11. Outline the potential medical uses of andrographis and English ivy leaf.
12. Analyze the available evidence for the use of peppermint, ginger, soy, and chamomile.

Faculty

A. José Lança, MD, PhD, received his Medical Degree at the University of Coimbra in Coimbra, Portugal, and completed his internship at the University Hospital, Coimbra. He received his PhD in Neurosciences from a joint program between the Faculties of Medicine of the University of Coimbra, Portugal, and the University of Toronto, Toronto, Canada. He was a Gulbenkian Foundation Scholar and was awarded a Young Investigator Award by the American National Association for the Research of Schizophrenia and Depression (NARSAD). (A complete biography appears at the end of this course.)

Faculty Disclosure

Contributing faculty, A. José Lança, MD, PhD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner/Director Disclosure

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

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

AACN Synergy CERP Category A.

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

DEFINITIONS

The National Center for Complementary and Integrative Health (NCCIH), a division of the U.S. National Institutes of Health, defines complementary and alternative medicine (CAM) as "health care approaches that are not typically part of conventional medical care or that may have origins outside of usual Western practice." [1]. Complementary medicine is non-mainstream practice used together with conventional medicine, and alternative medicine is non-mainstream practice used in place of conventional medicine. Integrative medicine attempts to bring together conventional and complementary approaches to health care [1]. CAM includes a wide range of products including natural health products (NHPs) and practices such as prayer, chiropractic, homeopathy, and massage therapy. In Canada, a similar definition is followed, and regulation of NHPs falls under the jurisdiction of the Natural and Non-Prescription Health Products Directorate (NNHPD), a branch of Health Canada [2].

Herbal medications (HMs), also known as phytochemicals or botanical medications, are considered an integral part of dietary supplements in the United States or natural health products in Canada [3]. Dietary supplements also include other natural compounds, such as vitamins, minerals, amino acids, and essential fatty oils [2].

PREVALENCE OF HERBAL MEDICATION USE

What percentage of adults in the United States use complementary/alternative medicine (CAM)?

The desire to maintain and promote individual health has contributed to the prevalent use of natural health products, including herbal medications. In 2012, more than 3 out of 10 adults (33.2%) in the United States used complementary medicine approaches and 17.7% used natural products other than vitamin and mineral supplements [1]. In Canada, an estimated 18% of the population takes natural products other than vitamin and mineral supplements [4].

Data from the National Center for Health Statistics (NCHS) indicate that supplement use among U.S. adults 20 years of age and older increased from 48.4% to 56.1% during the period 2007–2008 and 2017–2018, with use more common among women (63.8%) than men (50.8%) [5; 6; 7; 8]. Nonvitamin, nonmineral natural products are the most commonly used category of CAM (17.7%), followed by deep breathing (10.9%), yoga, tai chi, and qi gong (10.1%), chiropractic care (8.4%), meditation (8.0%), and massage therapy (6.9%). The NCHS also found that approximately 12% of children 17 years of age or younger use some form of CAM [5]. Considering the aging of the "baby-boom" generation and increased incidence of chronic health issues, it is likely that the use of CAM, and HMs in particular, will continue to increase in this group. In 2017–2018, dietary supplement use increased with age, both overall and in both sexes, and was highest among women 60 years of age and older (80.2%). The most common types of dietary supplements used were multivitamin-mineral supplements, followed by vitamin D and omega-3 fatty acid supplements [8].

The use of CAM for general health and well-being is greater in people with higher education and income, rather than in individuals with lower education and lower socioeconomic status [5; 9]. However, the National Health Interview Survey revealed that poor adults were more likely to use megavitamin therapy and prayer specifically for a health reason than not poor adults [10]. An estimated 13% of adult CAM users have indicated that they used CAM because conventional medicine was too expensive [10].

It is particularly relevant for medical practitioners that several studies have shown that more than 50% of patients who require conventional health care use CAMs separately or in conjunction with conventional therapies [9; 11; 12]. A published study of men with prostate cancer revealed that one-third of the patients used CAM in conjunction with their conventional therapy [13]. Of those, approximately 30% were taking vitamin and mineral supplements, while 40% were taking herbal compounds either alone or in conjunction with vitamins and antioxidants [13]. It has been estimated that 40% to 70% of patients using CAM fail to disclose this information to physicians or other healthcare professionals [5; 11]. Patients are more likely to disclose CAM use if it is provider-based rather than self-care use [9].

The prevalent use of herbal medications is particularly relevant to medical practice for three main reasons. First, it is commonly and erroneously assumed by patients that by being natural the compound is intrinsically beneficial and devoid of adverse effects. Second, patients often neglect to report to their physicians and other healthcare providers that they are taking HMs, as they think that it is not relevant. Third, pharmacologic interactions between compounds, regardless of whether they are from herbal or conventional origin, may alter therapeutic efficacies and cause negative interactions or serious adverse effects.

It is therefore essential to increase awareness regarding these issues and evaluate the pharmacologic profile and therapeutic properties of the most commonly used herbal medications based on scientific evidence, including clinical trials.

HISTORICAL OVERVIEW OF HERBAL MEDICATIONS IN NORTH AMERICA

Chemical compounds extracted from plants, animals, or micro-organisms, either in raw or purified form, have been used to treat disease for centuries and even millennia. Many of these substances are essential therapeutic tools and widely used in conventional medicine. Aspirin, digitalis, reserpine, morphine, most antibiotics, and anticancer drugs, to name but a few, are perfect examples of the long historical transition between natural medications and mainstream or conventional Western medications. The introduction of new and more effective conventional medications, such as statins, a class of drugs that inhibit 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity and effectively lower hyperlipidemia, and the antimalarial drug artemisinin, are pertinent examples of identification, extraction, and pharmaceutical application of natural compounds [14; 15]. In fact, it has been estimated that approximately 25% to 50% of marketed drugs are derived from natural sources [16]. One review found that almost 50% of the new small-molecule drugs introduced between 1981 and 2002 were natural products or their chemical derivatives [15]. Consequently, the difference between NHPs/HMs and conventional Western medications is not solely or primarily based on the origin of the compound (i.e., natural versus synthetic) but rather on the process of scientific evaluation of the pharmacologic and biologic properties, toxicologic profile, and therapeutic efficacy of a particular compound prior to its approval for marketing. In Western countries, the process of approval of new conventional drugs is tightly regulated. It falls under the jurisdiction of the U.S. Food and Drug Administration (FDA) in the United States; in Canada, it is regulated by Health Canada.

In the United States, herbal medications are considered dietary supplements and are regulated by the Dietary Supplement Health and Education Act (DSHEA) of 1994 [3]. Under this legislation, some claims, including structure and function, may be made by the manufacturer without requiring proof of safety and efficacy needed for conventional FDA-regulated medications. The product may be advertised as beneficial to maintaining or improving health of a particular organ or system, and the DSHEA states that the manufacturer is responsible for the safety of herbal products [3]. It is, however, the responsibility of the FDA to prove that an herbal compound is unsafe before a product is removed from the market [17]. This has been the case regarding the sale of dietary supplements, including HMs, containing ephedrine alkaloids (e.g., ephedra), which were prohibited in the United States by the FDA in April 2004 [18].

In Canada, herbal medications are classified as natural health products and fall under the jurisdiction of the Natural Health Products Regulations [19]. Canadian regulations provide a regulatory framework similar to the one existing in the United States. It is Health Canada's mandate to regulate the sale and safety of HMs, as illustrated by the ban on products containing ephedra in quantities greater than 8 mg per dose, 32 mg per day, or at any dose in combination with other stimulants, including caffeine.

MEDICAL AND PATIENT PERCEPTIONS AND MISCONCEPTIONS ABOUT THE USE OF HERBAL MEDICATIONS

What factors contribute to the inaccurate and biased perceptions of the use of HMs?

The pharmacology, therapeutic properties, and toxicologic potential of herbal medications are often the object of inaccurate and biased assessment. Numerous factors contribute to this situation. In some cases, healthcare providers may have limited formal training in the area, which can result in a limited appreciation of the beneficial properties of some phytochemicals and of their potential health risks, including pharmacologic interactions with conventional medications [20]. A survey of community pharmacists in Texas showed that in spite of the fact that 70% of new patients use CAM, pharmacists rarely ask patients about CAM use. This is a particularly troublesome occurrence considering the role played by the pharmacist in assessing potential interactions with conventional drugs [21].

A 2010 United Kingdom-based *Drug and Therapeutics Bulletin* (DTB) survey of 164 healthcare professionals, consisting mostly of hospital physicians and general practitioners, found that while a majority of physician participants (75.3%) considered HMs to be helpful in some circumstances, 72% indicated that the general public had misplaced faith in HMs and 86% felt the general public was poorly informed about HMs [22].

Patients often use herbal compounds based on the misconception that due to being natural, these products are intrinsically beneficial, do not cause adverse effects, and are devoid of any serious toxicologic potential. This is a widespread and inaccurate assessment. Patients need a better understanding of why informing their healthcare providers about CAM, and especially HM, use will be beneficial to their health.

In response to the increasing interest in CAM, including HMs, the U.S. Federation of State Medical Boards has approved guidelines for the use of CAM in conventional medical practice. This document provides information regarding "clinically and ethically responsible use of CAM, within the boundaries of professional practice and accepted standard of care," and provides the methodology to evaluate physicians' adherence to standards of medical practice required by state legislation [23].

CULTURALLY SENSITIVE ASSESSMENT

Because the use of CAM, including HMs, may be tied closely to cultural or ethnic traditions, it is important that any assessment for use of these products be undertaken with an understanding of possible barriers to disclosure. Pachter developed a dynamic model to facilitate culturally sensitive assessments, which involves several tiers and transactions [24]. The first component of Pachter's model calls for the practitioner to take responsibility for cultural awareness and knowledge. The professional should be willing to acknowledge that he/she does not possess enough or adequate knowledge in health beliefs and practices among the different ethnic and cultural groups he/she comes in contact with. Reading and becoming familiar with medical anthropology is a good first step.

The second component emphasizes the need for specifically tailored assessment [24]. Pachter advocates the notion that there is tremendous diversity within groups. For example, one cannot automatically assume that a Nigerian immigrant adheres to traditional beliefs. Often, there are many variables, such as level of acculturation, age at immigration, educational level, and socioeconomic status, that influence health ideologies. Finally, the third component involves a negotiation process between the patient and the professional [24]. The negotiation consists of a dialogue that involves a genuine respect of beliefs. The professional might recommend a combination of CAM and Western treatments. A knowledge of HMs commonly used in different cultures may allow healthcare professionals the opportunity to ask questions about specific products, as many patients do not volunteer information regarding their use of HMs.

DISCLOSURE AND CLINICAL NEED TO IDENTIFY THE USE OF HERBAL MEDICATIONS

As noted, an estimated 40% to 70% of patients fail to report the use of HMs to their physicians and other healthcare providers [5; 11; 13]. Some patients assume that reporting CAM use is not relevant because they are not mainstream medical products or procedures. In one literature review, the major reason for patients' failure to disclose the use of CAM was their concern of a negative reaction by the practitioner [11]. In the same study, lack of interest or assumed lack of knowledge by the medical practitioner were also reported among the main reasons for nondisclosure. This is supported by the 2010 DTB survey, which indicated physicians felt that their personal knowledge about HMs was "quite" or "very" poor (36.2% and 10.4%, respectively), and 89% conceded that their knowledge of herbal medications was "much poorer" than their knowledge of prescription drugs [22].

A number of patients do not disclose the use of HMs simply because their healthcare provider did not inquire [11]. While 77% of physicians worry that their patients may not be informing them about HM use, the DTB survey found that 9% never ask about HM use, 47% occasionally ask, 27% ask most of the time, and only 13% always ask [22]. Thus, considering the prevalent use and the common perception of healthcare professionals' attitudes toward herbal medications, it is essential to change these practices in order to safeguard patients' health.

CLINICALLY RELEVANT PHARMACOLOGY AND TOXICOLOGY OF HERBAL MEDICATIONS

What factors affect the concentration of active ingredients in HMs?

In North America, regulation of HMs is not as strict as that applied to conventional medications. In fact, good manufacturing practices applicable to food manufacturing are some of the only regulations in place to assure standards and quality control of dietary supplements [25]. The concentration of active ingredients in HMs, however, is affected by numerous factors, including [11; 26; 27; 28]:

- The correct identification of the botanical source
- The presence of contaminants or substitution of the intended source or other plants of lower cost with potential toxicologic consequences
- Growing conditions, including temperature, geography and time of harvest, and possible contamination with micro-organisms, heavy metals, pesticides, or prescription drugs
- Collection of the appropriate plant part (e.g., leaves versus root)
- Preparation of specimens (e.g., drying, grinding)
- Laboratory processing (e.g., solvent used for extraction of active ingredients)
- Storage
- Formulation of the final product (e.g., liquid versus solid pill)

These processes vary considerably among manufacturers and influence product quality and concentration of active ingredients in the final product.

Unlike most conventional medications, herbal products often have numerous active ingredients. Pharmacologic and chemical interactions between ingredients may be required for the product to be effective. Accordingly, isolation and purification of a single individual chemical may not lead to the same therapeutic effect as the one described for the original product.

PHARMACOKINETICS

Pharmacokinetics is the study of the effects exerted on drugs by the body, namely the processes of drug absorption, distribution, biotransformation, and ultimate elimination of drugs and their metabolites. All drugs ingested for nutritional, therapeutic, preventive, or diagnostic purposes, regardless of being of natural or synthetic origin, undergo processes of absorption and eventual distribution throughout body tissues and systems prior to reaching their molecular target. Drug distribution does not occur homogeneously throughout the body. Effective availability and concentration of a drug in different organs and tissues is influenced not only by the chemical properties of the drug (e.g., molecular size, electrical charge, ability to bind to plasma proteins, affinity for transporters that will carry the drugs across cell membranes) but also by the anatomic and histologic properties of the tissues themselves (e.g., degree of vascularization and type of capillaries present, including the tightly sealed blood-brain barrier).

Subsequently, all drugs undergo chemical transformation by the body. Briefly, drug transformation is carried out by enzymes leading to the production of metabolites that are either water-soluble (hydrophilic) and excreted mainly through the kidney, or lipid-soluble (hydrophobic). The latter are further metabolized in the liver mainly by a large family of enzymes known as cytochrome P450 (CYP450). Selective CYP450 isoforms, such as CYP3A4 and CYP3A5, are particularly relevant for clinical practice. In fact, CYP3A4 and CYP3A5 account for the metabolism of about 50% of all known drugs. For example, drugs such as digoxin, warfarin, indinavir, cyclosporine A, statins, and some calcium channel antagonists and anticonvulsants are metabolized by these isoforms. Increases or decreases in CYP450 activity therefore influence the processes of drug transformation, alter drug availability, and can have serious clinical implications [29].

PHARMACODYNAMICS

The pharmacologic and therapeutic properties of HMs and conventional medications result from the biologic interaction between an active compound and its target. The mechanisms underlying the drug-target interactions are studied in pharmacodynamics. The precise molecular mechanisms underlying the actions of HMs are, however, more difficult to establish due to the complex composition and presence of numerous chemical elements. For the most commonly used HMs, certain chemical elements have been isolated, their effects studied in vitro, and their therapeutic properties clinically evaluated. Allicin, for example, has been identified as the chemical ingredient in garlic responsible for its cardioprotective and plasma lipid-lowering properties. This effect correlates with the inhibition of HMG-CoA reductase by allicin and other disulfides present in garlic, which is a mechanism of action shared with statins [30; 31; 32].

The beneficial effects of saw palmetto in the treatment of benign prostatic hyperplasia (BPH) have been obtained with standardized lipidosterolic extracts. Several mechanisms of action have been reported, in both in vitro and in vivo models. Although saw palmetto has alpha 1-adrenoceptor antagonistic properties, a mechanism of action common to tamsulosin (Flomax), and anti-inflammatory properties because it inhibits cyclooxygenase, its beneficial effects on BPH correlate with its inhibition of 5-alpha-reductase. This latter mechanism is shared with the conventional drugs finasteride (Proscar) and dutasteride (Avodart) [33; 34].

DRUG INTERACTIONS

Drug-drug interactions, herb-drug interactions, and food-drug interactions can occur when different compounds are concurrently present in the body. These interactions can be either of a pharmacokinetic nature (i.e., absorption, distribution, metabolism, excretion) or a pharmacodynamic nature (i.e., interfering with the interaction between the drug and its molecular target, such as a receptor). Rarely, both pharmacokinetic and pharmacodynamic interactions may occur at the same time.

The complex composition of HMs can, in principle, become the source of various interactions. Multiple chemical compounds can interact either synergistically (i.e., increase the activity of one or more of its chemical constituents) or antagonistically (i.e., decrease the activity of one or more of its components). Furthermore, herbal remedies may include complex mixtures of several herbs, thereby significantly increasing the number of active compounds in the preparation. This makes it particularly difficult to ascertain which of the chemicals is pharmacologically responsible for a particular biologic event. The co-administration of HMs and conventional drugs further increases the possibility of interactions, which can be manifested during experimental conditions or clinically.

Herb-drug interactions apparently occur less frequently and are less serious than drug-drug interactions. This is due to the weaker potency of the herbal medications; however, interactions and adverse events may also be under-reported and relevant information may not be collected [35; 36].

Pharmacokinetic Interactions

Pharmacokinetic interactions between chemical compounds can alter the therapeutic properties of a drug and either increase or decrease the effectiveness of one or both compounds. For example, compounds in grapefruit and grapefruit juice strongly inhibit the liver enzyme CYP3A4 in a dose-dependent manner, thus reducing or preventing the biotransformation of drugs metabolized by this enzyme. This leads to abnormally high and potentially serious or lethal concentrations of these drugs in the blood [35]. Some clinically relevant interactions take place when grapefruit (as well as some other citrus varieties,

primarily sour types) are administered with statins, anxiolytic drugs, methadone, or calcium channel blockers [37]. This interaction has led to a ban of grapefruit products in many healthcare facilities.

Goldenseal, used topically as an antiseptic and systemically for the treatment of gastrointestinal disorders and menstrual pain, is also known to strongly inhibit CYP3A4, which prevents the metabolism of drugs such as erythromycin, leading to abnormally high blood levels of this antibiotic [38; 39].

An opposite effect is caused by other medications, including the herbal antidepressant St. John's wort (SJW). SJW induces both CYP3A4 and the intestinal drug transporter P-glycoprotein. Consequently, drugs transformed by CYP3A4 will be degraded faster and their blood levels quickly fall below therapeutic levels with foreseeable clinical implications [36]. These mechanisms have been linked to the low circulating levels of the antirejection drug cyclosporine in patients who received a kidney transplant and were also being treated with SJW [36]. A similar mechanism was reported in a heart transplant recipient and was responsible for the acute rejection of the transplant [40].

Other pharmacokinetic interactions between SJW and prescription drugs have been the subject of several clinical studies, including one that reported the interaction with the anxiolytic alprazolam [41]. Alprazolam is metabolized by CYP3A4 in the liver and intestinal mucosa, and SJW induced the activity of CYP3A4, shortening the elimination half-life of alprazolam from 12.4 to 6 hours.

Pharmacodynamic Interactions

Pharmacodynamic drug-drug or herb-drug interactions result from actions on molecular targets that mediate different processes of a physiologic response. The final result of these interactions can lead to an increase (i.e., synergism or potentiation) or decrease (i.e., inhibition or offset) of the expected response. For example, the antidepressant properties of SJW are associated with hypericin, pseudohypericin, and hyperforin. These compounds have a mechanism of action identical to fluoxetine (Prozac) and paroxetine (Paxil), and inhibit serotonin reuptake [42]. It is therefore not surprising that SJW, like the selective serotonin reuptake inhibitors, has a pharmacodynamic synergistic interaction with drugs that further contribute to increases in serotonin concentration in the synapse, such as monoamine oxidase (MAO) inhibitors (e.g., phenelzine) [41; 43; 44]. The abnormal increase of serotonin resulting from the herb-drug interaction can cause a mild "serotonin syndrome," characterized by confusion, restlessness, high blood pressure, fever, and muscle spasms [45; 46; 47; 48].

Clinically relevant interactions also occur between HMs and conventional medications that affect hemostasis, such as antiplatelet drugs (e.g., acetylsalicylic acid, dipyridamole), anticoagulants (e.g., heparin and vitamin K antagonists such as warfarin), and fibrinolytic drugs (e.g., alteplase, reteplase). A number of HMs contain high amounts of coumarin, salicylates, or other compounds that interfere with hemostasis. Both red clover (*Trifolium pretense*) and sweet clover (*Melilotus alba*) are rich in coumarin. Mold contamination of these plants converts the coumarin into dicoumarol, the vitamin K antagonist from which the potent anticoagulant warfarin is derived. Toxicity has been reported in cattle grazing on moldy clover hay [49; 50; 51]. Although this interaction has not been reported in humans, due to the below-threshold effect of dicoumarol when the herb is administered at the recommended dosage, it is advisable to closely monitor hemostasis in patients undergoing anticoagulant therapy [50; 51].

Another potential herb-drug interaction exists between ginkgo biloba and conventional anticoagulants, as a few cases of hemorrhage have been reported in the literature. One German study, however, has shown that the inhibition of the platelet-activating factor by ginkgo biloba was only observed for amounts at least 100 times higher than the recommended dose [52]. Although, mechanistically, there is the potential for synergistic interaction between ginkgo biloba and anticoagulants, it seems unlikely. Interactions between various HMs and conventional cardiovascular pharmacotherapy, such as anticoagulants, antihypertensives, diuretics, statins, and digoxin, have been reported [53].

ADVERSE EFFECTS/ADVERSE DRUG REACTIONS

As discussed, the pharmacologic properties of HMs and their interactions with prescription drugs can cause adverse effects, also known as adverse drug reactions, and have the potential to cause toxicologic effects. The reporting of adverse effects is the most important tool in post-marketing drug surveillance and accounts for 60% of the data used for adverse effects assessment [54; 55]. In the United States, the FDA has the FDA Adverse Event Reporting System (FAERS). Adverse event reporting for dietary supplements, including HMs, should be directed to FDA's MedWatch. The equivalent agency in Canada is the Canada Vigilance Adverse Reaction Online Database. Reports should be made to MedEffect Canada. An adverse events reporting system, Natural MedWatch, has also been established by the Therapeutic Research Faculty, an independent publisher of evidence-based recommendations for pharmaceuticals (***Resources***).

In both the United States and Canada, adverse effects can also be reported to the manufacturer. In turn, the manufacturer should submit all the collected information to the regulatory agencies. The efficiency of this latter process, however, has been the subject of lengthy debate.

TOXICOLOGY OF HERBAL MEDICATIONS

Systematic analysis of the evidence-based toxicologic properties of HMs is scarce. Toxicologic effects of HMs can result from:

- Administration of a high dose of an HM and consequent abnormal exacerbation of the intended therapeutic effect or occurrence of a toxic effect unrelated to the original therapeutic effect
- Adulteration of the product either by contamination with other plants or with prescription medications illegally included in the product
- Interactions with conventional drugs or other HMs

There is a relationship between the administered amount of a drug and the effect obtained (dose-response curve). As for any drug, very low doses of HMs, below the intended therapeutic threshold, do not have a pharmacologic effect, whereas higher doses within the therapeutic range will elicit the intended effect (therapeutic dose). Above therapeutic doses, the compound may elicit unintended responses, which can result from the exacerbation of the therapeutic effect and the accompanying adverse effects. For example, high doses of an antihypertensive drug can cause abnormally low blood pressure. Alternately, it may stem from the occurrence of another adverse effect not directly related to the primary therapeutic action of the drug. Acetaminophen, the leading cause of acute liver failure in the United States, is a typical example to illustrate the latter type of event [56]. When administered at doses above the therapeutic threshold for analgesia and antipyresis, it causes liver toxicity and can eventually cause death due to liver failure. The smallest dose of a drug that elicits a toxic effect is known as the minimum toxic dose. The lowest drug dose that causes death is known as the minimum lethal dose.

Considering the fact that HMs have a complex and varied chemical composition, and due to the limited knowledge of the precise effects on different constituents of organ systems, healthcare providers should always be aware of their potential toxicity. A relevant example results from chronic ingestion of germander (*Teucrium chamaedrys*). In traditional Chinese medicine, it is used in the form of tea or extract for a variety of purposes, including weight loss. A number of germander-induced cases of severe hepatotoxicity have been reported in the scientific literature, leading to it being banned in France [57]. In 1996, two more cases of hepatotoxicity were reported in Canada [58]. It has been established that its toxicity is caused by the development of autoantibodies that cause immunoallergic hepatitis, and it is strongly advised that it should not be ingested for any reason [59].

Toxicity may also occur as the result of adulteration in the composition of HMs. This may occur by contamination with toxic plants or molds due to improper selection or storage. Adulterations of the intended product may occur either accidentally or deliberately when unscrupulous suppliers replace the intended plant for a cheaper one. Although this substitution may cause physiologic responses that resemble the ones intended, other effects, including toxicity, may occur. Widely reported cases have occurred in several countries, including the United States, where a mixture of plants used in traditional Chinese medicine to detoxify the body contained *Digitalis lanata* instead of plantain and caused digitalis intoxication in two patients. More numerous cases were prevented by the timely intervention of the FDA, leading to the immediate recall of the product [60]. Another well-known case occurred in Belgium, where more than 40 patients developed interstitial fibrosis and progressive renal failure when the nephrotoxic herb *Aristolochia fangchi*, known to contain potent carcinogens, was substituted for the intended *Stephania tetrandra* [61].

On several occasions, it has been found that an HM was deliberately adulterated by adding a prescription drug. Such was the case reported in England, when very high levels of the synthetic drug dexamethasone were found in an herbal cream used to treat eczema [62]. In Saudi Arabia, a complete toxicologic screening of more than 200 samples of traditional products revealed contamination by synthetic drugs (8 cases), micro-organisms (18 cases), toxic substances of natural origin (14 cases), or high heavy metals content (39 cases) [63]. These examples illustrate the need for an increased public and professional awareness, the implementation of appropriate quality control and exhaustive testing of supplies, adherence by the manufacturers to good manufacturing practices, and selection of products manufactured by reputable companies [64].

HERBAL MEDICATIONS: REGULATORY ASPECTS

COMPARISON OF THE PROCESSES OF APPROVAL OF HERBAL COMPOUNDS AND CONVENTIONAL DRUGS

How does the mechanisms required for the marketing of HMs compare to the process required for pharmaceutical approval in the United States?

As mentioned, the main difference between HMs and conventional Western medications is neither exclusively nor primarily based on the origin of the compound (i.e., natural versus synthetic) but rather on the process of evaluation regarding efficacy and safety, which the compound should undergo prior to being marketed. In fact, many conventional medications are extracted from natural sources or are the chemical derivatives of naturally occurring molecules.

In Western countries, the process of approval of new conventional medications is tightly regulated. New drugs undergo a process of detailed scrutiny and scientific evaluation prior to being released into the market. Briefly, during the preclinical stages, the physiopathologic mechanisms underlying the disease are identified, and biologic targets (e.g., enzyme, receptor, gene) are identified. Drugs aimed at biologic targets are tested in vitro, and in vivo experiments are conducted under controlled conditions. When the potential therapeutic benefit has been established based on the preclinical studies and the drug is considered ready for human studies, an elaborate application is then submitted to the appropriate regulatory institution: the FDA in the United States and Health Canada in Canada. The application includes:

- Composition and source of the drug
- Manufacturing information
- Data from in vitro and animal studies
- Detailed plans for proposed clinical trials
- Names and credentials of physicians responsible for conducting the clinical trials

If approved, human studies of the investigational new drug (IND) can be initiated. At the institutional level, interdisciplinary review boards are responsible for assuring the ethical and scientific integrity of the clinical trials.

Clinical studies are conducted in four stages or phases (I, II, III, and IV). Phase I is aimed at establishing drug safety, dosage, and pharmacokinetic properties of the drug (e.g., half-life, metabolism). These are open or nonblind studies, in which both investigators and healthy subjects (25 to 100) know what is being administered. Results of human studies are compared with animal studies.

The goal of Phase II is to study the effect of the drug on volunteer patients (100 to 200) with the disease for which the drug was developed. Subjects will either receive the drug, a placebo (negative control), or the standard drug (positive control) used in the treatment of the disease. Further toxicologic studies in animals will continue to assess chronic toxic potential.

Finally, in Phase III, double-blind or cross-over studies are conducted to further evaluate the efficacy of the drug in larger groups of thousands of patients. When Phase III is finished and if the results meet the goals initially established, a new drug application (NDA) will be submitted to the FDA or its congener in another country. After several years of preclinical research, four to six years of clinical trials, and as many as three years after the NDA has been submitted, the FDA may then approve marketing of the drug. At that point, Phase IV is initiated and a mechanism of post-marketing surveillance, including reporting of adverse effects, will be in place.

Compared with this elaborate process of approval, the mechanisms required for the marketing of HMs are extremely simple. To start, in many Western countries, including the United States and Canada, herbal medications are not legally considered drugs, but rather as dietary supplements and natural health products, respectively. Consequently, HMs are not legally required to undergo extensive preclinical investigation, and clinical trial evaluations are not required prior to the marketing of the herbal product. Rather, approval is based on traditional usage.

It should be noted that several herbal medications, namely in the European community, have been thoroughly evaluated, including safety and efficacy, product standardization, and well-conducted clinical trials with comparison to standard treatments (i.e., Phase III). These principles apply to the studies conducted to evaluate the efficacy of standardized preparations of saw palmetto (*Serenoa repens*) in the treatment of BPH [33; 34; 65].

SCIENTIFIC EVALUATION OF HERBAL MEDICATIONS

PRECLINICAL STUDIES AND EVALUATION IN CLINICAL TRIALS

Which measures contribute to an evidence-based approach to HMs?

The number of scientific studies aimed at unraveling the mechanism of action of HMs has undergone a remarkable growth in recent decades. Development of new legislation, availability of research funds to study the pharmacologic mechanisms of action and therapeutic efficacy of HMs, drug standardization, and implementation of clinical trials to assess HMs have played a central role in the development of an evidence-based approach to phytotherapeutics. The NCCIH in the United States and the NNHPD in Canada are pivotal in establishing advisory panels, coordinating scientific resources and expertise, and funding quality research on HMs [64; 66]. The American Society for Pharmacology and Experimental Therapeutics has long supported the increase in the National Institutes of Health's NCCIH budget for peer-reviewed research on botanical medications, particularly aimed at studying mechanisms of action and interactions with prescription drugs [67].

Scientific evidence on HMs should also be included in the basic curriculum in medical, pharmacy, dental, and nursing schools. Continuing education of healthcare professionals also contributes to a multidisciplinary and inclusive evidence-based assessment of HMs as part of a broader approach to maintenance of health and disease prevention.

IDENTIFICATION OF ACTIVE COMPOUNDS, ISOLATION, AND STANDARDIZATION

Standardization of the product and its individual chemical constituents is of major importance, and reliability of practices and procedures by the manufacturer is absolutely crucial. Several reports have analyzed the concentration of active ingredients present in herbal medications and compared the values obtained with those reported on the label by the manufacturer. Batch-to-batch variability has also been reported, and in one particular case of a compound containing ephedrine and methyl ephedrine, concentration of these substances varied by 180% and 1,000%, respectively [68].

The lack of standardization may also account for negative results obtained in some clinical trials [69]. One study revealed that, in the case of the antidepressant SJW (*Hypericum perforatum*), the amount of two of its most important chemical constituents, hypericin and pseudohypericin, can vary from 108% to 30% or even to as little as 0.1% of the amount reported on the label when a chemical analysis is conducted in a large number of samples from various manufacturers [70].

More reassuring results have been reported. The chemical composition of five of the most commonly used HMs was studied, and these results were compared to the information provided in the label by the manufacturer [71]. Results of this study, conducted by the University of California, Los Angeles (UCLA) Center for Human Nutrition, are encouraging and reflect a positive trend in increased quality and standardization of HMs by the manufacturers. For each product, three different samples from each of 12 bottles (6 bottles for each of the two separate batches) were collected. Five of the most commonly used HMs in North America were studied, specifically saw palmetto, SJW, echinacea, ginkgo biloba, and kava. Samples were purchased from 8 to 10 different suppliers nationally available in the United States. A greater consistency of composition was observed for samples purchased over the counter than for those purchased by mail order. A drastic decrease in variability of the marker compound was observed between batches; saw palmetto and SJW were the least variable, and the most variable were ginseng and echinacea [71].

In fact, analysis of the saw palmetto specimens revealed that the concentration of the marker compound ranged from 77% to 106%, and for two of the manufacturers the values were within ±10% of their label claim. For SJW, the concentration of the marker compound hypericin ranged from 88% to 110%, and for two of the suppliers it was within ±10% of their claim. In the echinacea compounds studied, the concentration of the marker compound ranged from 78% to 173% of the reported value, and two of the manufacturers were within ±10% of the concentration claimed. Ginseng was the most variable HM, and the amount of the marker varied from 44% to 261% of the claim. Only for one of the manufacturers was the value within ±10% of the claim. For kava, the values were within ±10% of their claim for more than 70% of the suppliers [71].

In the United States, the National Institute of Standards and Technology (NIST), in collaboration with the National Institutes of Health Office of Dietary Supplements, the FDA, the Center for Drug Evaluation and Research, and the Center for Food Safety and Applied Nutrition, is developing procedures regarding the standardization of dietary supplements and natural health products [64; 72]. The development of standardization of active ingredients, accurate evaluation of chemical contaminants, such as toxic metals present in the soil and/or acquired during processing, and screening for microbiologic contaminants, such as *Escherichia coli*, will certainly contribute to an increase in consumer reassurance, and to the acceptance by larger numbers of conventional healthcare providers [73]. In 2007, the FDA issued guidelines to outline requirements and expectations regarding how dietary supplements are manufactured, prepared, and stored [74]. These practices are meant to reduce misidentification and contamination of dietary supplements by manufacturers and to reduce errors in purity, strength, and composition. The guidelines are updated periodically to ensure current safe practices, with the last update conducted in 2013 [74; 75]. Although the practices are expected to be adhered to, to date there is no FDA approval process [74]. Several organizations, including the U.S. Pharmacopeial Convention (USP), NSF International, and Consumerlab.com, offer voluntary dietary supplement verification programs that provide standards and monographs for determining product and ingredient identity, strength, quality, and purity, and award a seal of approval mark to dietary supplement products that meet their criteria [74; 76; 77; 78].

Legislation requiring the standardization of herbal medications has been successfully implemented in several countries of the European Union, with benefits regarding the scientific assessment of pharmacologic properties and conduction of well-controlled clinical trials and mandatory reporting of adverse effects [79]. It has often been argued that a stricter control of phytochemicals further enhances their role as useful complementary rather than alternative therapeutic tools to conventional medications [64; 74; 75].

EVIDENCE-BASED REVIEW OF THE MOST COMMONLY USED HERBAL MEDICATIONS

Considering the large number of available HMs, it is beyond the scope of this course to exhaustively review them all. Fourteen of the most commonly sold HMs will be reviewed following an evidence-based assessment of several parameters relevant to clinical practice (***Table 1***). For each phytomedicine, the following subjects will be presented:

- Common name and scientific name
- Historical and current use
- Pharmacology

A REVIEW OF HERBAL MEDICATIONS				
Common Name	**Scientific Name**	**Typical Modern Uses**	**Efficacy**	**Safety**
Saw palmetto	*Serenoa repens* or *Sabal serrulata*	Treatment of benign prostatic hyperplasia (BPH)	★★E	S
St. John's wort	*Hypericum perforatum*	Treatment of mild-to-moderate depression	★★E	AEs/DIs
Ginkgo	*Ginkgo biloba*	Management of age-related memory loss, dementia, early stages of Alzheimer disease	★★E	S
Ginseng	*Panax ginseng, P. quinquefolius, P. japonicus*	Treatment of cardiovascular diseases, diabetes, immunomodulation, menopause	★E	No S data
Echinacea	*Echinacea angustifolia, E. pallida, E. purpurea*	Treatment of common-cold symptoms	★★E	S
Kava	*Piper methysticum*	Treatment of anxiety, stress, insomnia	★★★E	AEs/DIs/UnS
Garlic	*Allium sativum*	Prevention and treatment of hyperlipidemia, hypertension, cardiovascular disease	★★E	AEs/DIs
Valerian	*Valeria officinalis*	Treatment of insomnia, anxiety	★★E	S
Andrographis	*Andrographis paniculata*	Prevention of upper respiratory tract infections	★★E	AEs/DIs
English ivy leaf	*Hedera helix*	Treatment of bronchitis and asthma	★★★E	S
Peppermint	*Mentha x piperita* Lamiaceae	Management of irritable bowel syndrome, dyspepsia	★★E	S
Ginger	*Zingiber capitatum* or *Zingiber officinale*	Treatment and prevention of nausea	★★★E	S
Soy	*Glycine max*	Treatment of cardiovascular disease, osteoporosis	★E	No S data
Chamomile	*Chamaemelum nobilis* or *Matricaria recutita*	Management of inflammatory diseases	★★E	S

Source: Compiled by Author *Table 1*

- Evidence-based therapeutic use and effectiveness
- Adverse effects and drug interactions
- Toxicology
- Dosage

The therapeutic effectiveness of each medication is based on published scientific data regarding in vitro and in vivo studies of the mechanism of action and clinical studies, including randomized clinical trials, clinical studies, and meta-analyses. Accordingly, each herbal product is ranked into one of the following four categories:

★★★E: Clinically effective: Demonstrated by multiple randomized clinical trials

★★E: Clinically beneficial: Demonstrated by several controlled clinical trials, although some studies show conflicting or inconclusive results

★E: Limited effectiveness: Demonstrated by controlled clinical trials

No E data: Nonexistent or minimal supporting scientific evaluation

Product safety guidelines follow the same general rules applicable to mainstream drugs, and use during pregnancy, lactation, and childhood should be restricted to compounds tested for teratogenicity, carcinogenicity, and general toxicity. Otherwise, it is not advisable for the patient to be exposed to an untested HM. As a guideline, a product is ranked as:

- **S**: Safe
- **AEs/DIs**: Reported adverse effects and/or drug interactions
- **UnS**: Unsafe
- **No S data**: Unknown or limited controversial safety data

SAW PALMETTO

Efficacy: ★★E

Safety: S

Common Name and Scientific Name

Saw palmetto (*Serenoa repens or Sabal serrulata*) is also known as American dwarf palm or cabbage palm. This abundant and scrubby palm is indigenous to Florida and other southeastern states of the United States.

Historical and Current Use

Saw palmetto berries collected in the autumn were used by southeastern Native Americans in the treatment of urinary disorders and as an antiseptic. Saw palmetto extracts are now used in the treatment of BPH. In several European countries, use of this herb has been approved for the treatment of mild-to-moderate BPH. In Germany and Austria, saw palmetto is the most common form of therapy for BPH and represents more than 90% of all drugs prescribed for the treatment of this disorder [51; 65].

Pharmacology

The beneficial effects of standardized liposterolic extracts (phytosterols) in the treatment of BPH are now well established. The extracts represent 85% to 95% of free fatty acids from saw palmetto berries. Although the mechanism of action of saw palmetto is not completely understood, both in vitro and in vivo studies have revealed that the beta-sitosterol component of the extract correlates with its efficacy in the treatment of BPH [80; 81; 82]. Saw palmetto inhibits 5-alpha-reductase, the enzyme responsible for the transformation of testosterone into dihydrotestosterone (DHT), its tissue-active form [82; 83]. This mechanism of action is similar to the one described for finasteride and dutasteride [34; 82; 84]. It should be noted, however, that finasteride only inhibits the type 1 isoform of 5-alpha-reductase responsible for the production of different testosterone metabolites in the tissues, whereas saw palmetto inhibits both type 1 and type 2 isoforms [82; 85].

Other pharmacologic mechanisms of action of saw palmetto have been reported in the literature, namely that it competes with DHT and blocks androgen receptor stimulation, although this mechanism does not seem to correlate with its clinical efficacy [82; 86]. In vitro, saw palmetto extracts have alpha-1 adrenoceptor blocking properties like the standard drug tamsulosin, albeit this mechanism does not seem to account for saw palmetto's therapeutic effects as it is not observed at the lower concentrations, which are equivalent to the doses used in humans [87]. Interestingly, saw palmetto also inhibits cell proliferation and promotes apoptosis (i.e., programmed cell death) of prostate cancer cells, and its anti-inflammatory properties have been linked to its inhibitory actions on cyclooxygenase and lipoxygenase [88; 89; 90]. Together, all of these mechanisms may synergistically contribute to the therapeutic efficacy of saw palmetto extracts.

Evidence-Based Therapeutic Use and Effectiveness

The clinical effectiveness of saw palmetto in the treatment of mild-to-moderate BPH has been extensively studied. A comprehensive review of clinical studies that assessed the efficacy of saw palmetto versus placebo and saw palmetto versus finasteride was published in 2002 [65]. Results from 21 clinical trials, with a total of more than 3,000 patients, were analyzed. Several clinical parameters were evaluated, including urinary symptoms (e.g., dysuria, fullness, bladder residual volume), nocturia, urine flow rate, and prostate size (Boyarsky score, American Urologic Association Score, and International Prostate Symptom Score). The authors concluded that, "men taking saw palmetto were nearly twice as likely to report improvement in symptoms than men taking placebo," [65]. Also, "when compared to finasteride, saw palmetto provided similar responses in urologic symptoms and flow measures and was associated with a lower rate of impotence" [65]. This review, however, lacks information regarding comparisons between saw palmetto and alpha-1 adrenoceptor antagonists such as tamsulosin. Updates of this review, published in 2009 and 2012, found that saw palmetto was not more effective than placebo for treatment of urinary symptoms consistent with BPH [91; 92].

A large study of more than 2,500 patients suffering from mild-to-moderate BPH compared the effectiveness of saw palmetto versus tamsulosin (704 patients), saw palmetto versus finasteride (1,098 patients), and two different doses of saw palmetto (160 mg twice a day versus saw palmetto 320 mg once a day) [34]. The study demonstrated a better outcome for patients taking saw palmetto than those taking either of the conventional drugs. Also, unlike the conventional drugs, no negative impact on sexual function was reported by patients treated with saw palmetto. These results further support other well-conducted studies [84; 93; 94; 95; 96; 97; 98; 99; 100]. Interestingly, saw palmetto was less effective than finasteride in reducing prostate volume, although involution of the prostate epithelium and reduction of inflammation was observed [34; 101]. Co-administration of saw palmetto and finasteride did not improve the treatment outcome. A report in which saw palmetto efficacy was not observed may be attributable to the study being conducted in patients with moderate-to-severe BPH, as opposed to the beneficial effects on patients with a mild-to-moderate condition [102]. In addition to the population cohort difference, the study also failed to conduct an appropriate dose-response study or raise the dose of saw palmetto to adjust for the severity of the medical condition.

In conclusion, evidence demonstrates that saw palmetto is effective in the treatment of mild-to-moderate BPH, is less expensive, and is better tolerated than conventional medications [94; 103]. In addition, it is now well established that saw palmetto does not interfere with the laboratory measurements of prostate specific antigen (PSA), used to assess the progression of prostate cancer [83; 104]. This presents a considerable advantage over 5-alpha-reductase inhibitors finasteride and dutasteride, which are known to mask PSA readings and prevent an accurate assessment of the disease progression and concurrent development of prostate cancer [83; 104]. The efficacy of saw palmetto in the treatment of more severe BPH has not been established.

Saw palmetto has also been used to treat other genitourinary disorders, including chronic prostatitis. However, clinical studies have shown a lack of significant improvement in patients treated with saw palmetto for one year, contrasting with the benefits observed in the group treated with finasteride [103; 105].

It has also been advocated that saw palmetto, either alone or in conjunction with other nutraceuticals, may also play an important role in the prevention of BPH, although the results obtained are inconclusive [106; 107]. The effects of chronic saw palmetto administration on the organization of chromatin structure in patients with BPH provides an insight of the molecular effects of saw palmetto potentially relevant to gene expression and tissue differentiation [108].

Adverse Effects and Drug Interactions

Consistently, all studies revealed the absence of significant side effects. A 2008 meta-analysis of saw palmetto trials found that serious adverse effects (e.g., cancer, sexual dysfunction, hepatotoxicity, respiratory problems) were no more common in treatment groups than in placebo groups [109]. Gastrointestinal symptoms, including nausea or abdominal pain, may occur in less than 2% of patients but seem to decrease when doses are taken with a meal. Because of its antiandrogenic properties, women should not take saw palmetto for treatment of urogenital problems if they take contraceptives, hormone replacement therapy, have breast cancer, or are pregnant [65; 82]. Furthermore, there is no clinical evidence supporting a beneficial effect of saw palmetto in the treatment of urethritis in women. Interactions with anticoagulants are negligible and arise from a single reported case [110]. In clinical trials, 3% of the subjects developed hypertension, compared with 2% treated with finasteride; however, this difference was not statistically significant [84].

Toxicology

Saw palmetto is widely considered a safe phytomedicine, and no serious toxicologic effects are reported in the scientific literature [109]. Results of the Complementary and Alternative Medicine for Urological Symptoms (CAMUS) trial found no evidence of toxicity among 369 patients randomized to 320 mg, 640 mg, or 960 mg daily saw palmetto extract at doses up to three times the usual clinical dose during an 18-month period [111].

Dosage

Standardized lipophilic extracts of saw palmetto are administered at a dose between 100–400 mg twice daily for the treatment of BPH [33; 34; 51; 82]. A dose of 160 mg twice a day is the most commonly used dosage in clinical trials [82]. Therapeutic benefits are observed within three to four weeks after the initiation of treatment, which usually lasts for three to six months.

ST. JOHN'S WORT

Efficacy: ★★**E**

Safety: **AEs/DIs**

Common Name and Scientific Name

St. John's wort (*Hypericum perforatum*) is also known as amber touch-and-heal, goatweed, and klamath weed.

Historical and Current Use

This perennial, native to Europe, Western Asia, and North Africa, is a resilient weed, widespread in parts of the United States and southern Canada. The plant has golden-yellow flowers that bloom in the summer, which are collected and dried. The medicinal use of SJW as a topical anti-inflammatory and for wound healing has been known since ancient Greece. Extracts have been used in folk medicine for the treatment of depression and other mood disorders and also as a diuretic. Today, SJW is used primarily for the treatment of mild-to-moderate depression and has traditionally been the most commonly prescribed antidepressant in Germany, where it is available as a prescription medication [79; 112].

Pharmacology

What pharmacologic mechanisms of action of St. John's wort extracts are relevant to their antidepressant effects?

Several chemicals, including naphthodianthrones (e.g., hypericin, pseudohypericin), phloroglucinols (e.g., hyperforin), flavonoids (e.g., quercetin), and essential oils, are the primary constituents of SJW [82; 113]. Formulations are standardized to concentrations of hypericin, usually 0.3% to 0.4%, which is considered the active ingredient responsible for the antidepressant properties of SJW. Clinical and pharmacologic studies, however, have shown that hyperforin concentrations of 2% to 4% correlate closely with antidepressant efficacy [114; 115].

The pharmacologic mechanisms of action of SJW extracts relevant to its antidepressant effect are complex. Hypericin may have a minor role in MAO inhibition, a mechanism shared with the classical antidepressant phenelzine [82]. This mechanism, however, is not considered clinically significant because it is only observed at concentrations 100 times higher than those used to treat depression [33]. Hyperforin is generally agreed to be the active component [82]. Both hypericin and hyperforin inhibit synaptic reuptake of serotonin, which is the same action as fluoxetine and paroxetine, but they also inhibit the reuptake of dopamine and noradrenaline, like other antidepressants including venlafaxine [82; 116].

After a single dose, the half-life of hypericin is four to six hours, whereas after chronic administration, the half-life of hypericin is one to two days [117; 118]. These values are comparable to those observed for fluoxetine (one to three days) and the selective serotonin re-uptake inhibitor (SSRI) paroxetine (12 hours) [48].

Long-term administration of SJW extracts increase the synaptic density of serotonin receptors by 50%, whereas the receptor affinity remains unchanged [119]. The increase in number of serotonin receptors was observed after a minimum 10 to 12 days treatment, a time frame that correlates with the well-known therapeutic delay of standard antidepressant drugs [120]. Together, the increased number of serotonin receptors and the increase in synaptic concentrations of neurotransmitters provide a mechanistic explanation for the antidepressant effects of SJW [113; 117; 121].

SJW extracts also have antibacterial properties, accounting for the antiseptic and wound-healing properties of topical formulations. Hyperforin is effective in inhibiting gram-positive bacteria, including penicillin-resistant and methicillin-resistant *Staphylococcus aureus*, but it is not effective against gram-negative bacteria. One randomized trial showed the effectiveness of SJW topical application in the treatment of atopic dermatitis [122; 123; 124]. In one small pilot study, SJW significantly improved erythema, scaling, and thickness in plaques of patients with mild psoriasis [125].

Some in vitro studies have shown that SJW extracts have antiviral properties, namely against influenza virus, and one study has identified a novel protein in SJW that suppresses gene expression in human immunodeficiency virus (HIV) [122; 126]. However, a Phase I clinical trial provided negative results [127]. It is important to emphasize that SJW should not be administered to HIV or acquired immune deficiency syndrome (AIDS) patients because of the pharmacokinetic interactions with antiretroviral protease inhibitors, such as indinavir, saquinavir, and ritonavir, and non-nucleoside reverse transcriptase inhibitors, such as efavirenz, which are metabolized by CYP3A4. Induction of CYP3A4 by SJW drastically reduces drug concentrations in the blood by 50% to 80% with subsequent loss of HIV suppression [128].

Finally, in vitro studies have shown that hyperforin and hypericin inhibit tumor cell growth by induction of apoptosis [129; 130]. The use of SJW extracts in the treatment of triple-negative breast cancer is an area of ongoing research [131; 132]. Although these compounds seem to have high efficacy, their potential clinical usefulness as anticancer agents is, at this point, merely speculative.

Evidence-Based Therapeutic Use and Effectiveness

Several clinical trials have assessed the efficacy and safety of SJW preparations in the treatment of depression. A 2005 Cochrane Review extensively analyzed published randomized, double-blind trials comparing SJW with placebo (26 studies) or with standard antidepressants (14 studies) [133]. SJW was demonstrated to be "more effective than placebo and similarly effective as standard antidepressants for treating mild-to-moderate depressive symptoms" [133]. The treatment period lasted from 4 to 12 weeks.

Two large clinical trials conducted in the United States did not support these findings [134; 135]. Both studies were conducted on patients who suffered from moderate-to-severe depression, and many patents presented with a history of drug-resistant depression, which may have affected the outcomes. The Hypericum Depression Trial Study Group has also been criticized because the response rates for both the SJW-treated and the sertraline-treated groups were not different from the placebo-treated group. In another randomized study, conducted in Germany, the effect of SJW (900 mg/day standardized SJW extract) on moderate-to-severe depression was compared with paroxetine (20 mg/day) [42]. The treatment was continued for 6 weeks, and in initial non-responders, after 2 weeks of treatment the doses were increased by 100%. The results indicated that, in the treatment of moderate-to-severe depression, hypericum extract was, "at least as effective as paroxetine" and was better tolerated [42]. A 2008 Cochrane Review of trials examining the treatment of severe depression with hypericum reached similar conclusions as to its efficacy in comparison to placebo and conventional antidepressants. Also, subjects in the SJW groups had a lower drop-out rate, possibly due to fewer side effects [136].

It is established in the scientific literature that standardized SJW extracts are effective and safe in the treatment of mild-to-severe depression [51; 122; 133; 136; 137; 138; 139].

Adverse Effects and Drug Interactions

SJW is well-tolerated and generally safe. Mild side effects include gastrointestinal symptoms, mild sedation or tiredness, dizziness, headache, and dry mouth. Incidence of side effects in SJW-treated patients (4% to 12%) is similar to that observed in the placebo-treated group and significantly lower than standard antidepressants [51; 82; 140; 141]. Two rare adverse events may occur after administration of SJW. First, transient photosensitivity may occur when administered in higher doses,

and second, the occurrence of a serotonin syndrome when co-administered with SSRIs is possible [82; 142]. The latter results from the synergistic interaction between the drugs raising serotonin to abnormally high levels [45; 46; 47; 48; 143].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Psychiatric Association, St. John's wort may be considered for patients with major depression who prefer complementary and alternative therapies, although evidence for its efficacy is modest at best and careful attention to drug-drug interactions is needed.

(https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Last accessed June 10, 2022.)

Strength of Recommendation: III (May be recommended on the basis of individual circumstances)

Pharmacokinetic interactions with SJW are rare and only occur at higher doses. Induction of cytochrome P450 isoforms, namely CYP3A4 and CYP1A2, by SJW results in a decreased bioavailability of drugs metabolized by this liver enzyme. These drugs include the immunosuppressant cyclosporine, the anticoagulant warfarin (bleeding), oral contraceptives (causing breakthrough bleeding), antiretroviral protease inhibitors, and theophylline [36; 51; 82; 128; 138]. A report has also shown a reduction in plasma levels of the HMG-CoA reductase inhibitor simvastatin [144]. Activation of the intestinal P-glycoprotein transporter also accounts for the reduction in plasma concentrations of digoxin [128].

In conclusion, although SJW has consistently been reported to be a safe drug when administered within its therapeutic range, its potential interactions with other drugs or herbs (e.g., kava) require caution and a thorough investigation during patient interview prior to use.

Toxicology

It is widely accepted in the literature that, when used within the normal therapeutic range, SJW is devoid of toxicologic properties. In high doses, SJW can elicit photosensitivity. Phototoxicity results from light-induced transformation of hypericin-derived pigments and has been reported in patients with HIV receiving high doses of intravenously administered SJW [127]. To date, only one study of potential teratogenicity during human pregnancy has been conducted, with data collected from the pregnancies of 54 SJW-treated women and 108 women either treated with conventional antidepressants or receiving no pharmacologic treatment. Rates of fetal malformations were similar among the three test groups and similar to rates of malformations in the general population; additionally, premature and live birth rates among the three test groups were similar [145]. Further research in this area is needed, and SJW administration in pregnant patients should therefore be avoided [82].

Dosage

Standardized preparations of SJW are usually administered from 500–1,800 mg per day [51; 122; 133; 137; 138]. In most studies, 900 mg was administered daily (450 mg twice a day, or 300 mg three times a day) [82].

GINKGO

Efficacy: ★★**E**

Safety: **S**

Common Name and Scientific Name

Ginkgo (*Ginkgo biloba*), also known as kew tree, ginkyo, or duck-foot tree (because of the characteristic fan-shaped leaves), is a large, resilient, and long-living tree cultivated by monks in China, where many individual specimens are documented to be more than 1,000 years old. Ginkgo trees, often known as living fossils, are the only survivors of the entire Ginkgoaceae family. Fossils of this tree that date back more than 200 million years have been identified in areas throughout the Northern Hemisphere, including Europe and North America. Ginkgo trees were brought into Japan and other East Asian countries around 1200 C.E., possibly in relation to the spread of Buddhism. In the seventeenth century, they were reintroduced in Europe and, more recently, in North America. Ginkgo is a resilient tree to parasites and diseases and, interestingly, also survived the Hiroshima atomic bombing.

Historical and Current Use

The designation originates from ginkgo, meaning silver apricot, and biloba, which describes the two-lobed shape of the leaf. Historically, leaf extracts have been used in traditional Chinese medicine to treat a variety of disorders, including asthma, allergies, premenstrual syndrome, tinnitus, cognitive impairments resulting from aging and dementia, and vascular diseases including central and peripheral vascular insufficiencies. Standardized leaf extracts are used based on their neuroprotective and vascular regulatory properties in the management of intermittent claudication, age-related memory loss, dementia, and early stages of Alzheimer disease [33; 146]. Plum-like fruits of the female tree are not edible and cause contact dermatitis. Ingestion of the seeds causes headache, nausea, diarrhea, and even seizures when ingested in larger amounts [51; 147].

Pharmacology

More than 40 chemical components of ginkgo have been isolated, including flavonoids, terpenoids, flavones, catechins, sterols, and organic acids. The two most important and active groups of chemicals are the flavonoids, such as quercetin and kaempferol, and the terpenoids, including ginkgolides A, B, C, J, and M and bilobalide. Ginkgo biloba extracts available in Europe and North America are standardized to 24% flavonoids and 6% terpenoids and have been used in hundreds of in vitro and in vivo studies and numerous clinical trials [33; 51].

The biologic properties of ginkgo biloba extract result from the complex interactions among chemical components, and it is therefore difficult to establish a well-defined cause-effect relationship between specific elements and biologic effect. Nevertheless, it is now well established that flavonoids have antioxidant and free-radical scavenger properties. They also have a protective effect against apoptosis and beta-amyloid neurotoxicity of Alzheimer disease and may play an important role in the prevention of neuronal degeneration in Parkinson disease [148; 149; 150; 151].

Terpenoids, particularly ginkgolides, inhibit the platelet activating factor (PAF), and therefore prevent platelet aggregation, have anti-inflammatory properties, and prevent contraction of smooth muscles in the respiratory tract [146]. The vasodilatory properties of standardized ginkgo biloba extract preparations are attributed to the stimulation of endothelium-derived relaxing factor and regulation of nitric oxide release [51].

Ginkgo biloba extract also stimulates receptor expression and neurotransmitter concentrations in the brain, particularly acetylcholine [152; 153; 154; 155]. This latter mechanism of action is similar to the cognitive enhancer, tacrine, previously used in the treatment of Alzheimer disease [156].

Evidence-Based Therapeutic Use and Effectiveness

There is scientific evidence supporting the beneficial use of standardized ginkgo biloba extract, 120–240 mg/day, in the treatment of mild-to-moderate cognitive impairment, such as age-related dementia, multi-infarct dementia, and possibly Alzheimer disease [33; 157; 158; 159]. Some studies show that ginkgo biloba extract is as effective as the acetylcholinesterase inhibitor donepezil (Aricept) in the treatment of patients with early stages of Alzheimer disease, although these findings are not supported by additional studies [160]. One study reported that the combination therapy of gingko biloba extract plus donepezil was more effective than either therapy alone [161]. A 2015 systematic review noted a positive response (defined as improvement in cognitive function and activities of daily living and reduced neuropsychiatric symptoms) to a 240 mg/day dose in study participants with neuropsychiatric symptoms related to a dementia diagnosis but not in individuals thought to have Alzheimer disease [159]. Although studies have shown that ginkgo biloba extract appears to be safe and with no excess side effects compared with placebo, the evidence that it has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent, and whether ginkgo biloba leaf extract is beneficial for the treatment of Alzheimer disease remains controversial. Researchers recommend that the findings be confirmed by larger clinical trials [33; 162; 163; 164; 165; 166; 167; 168].

Clinical trials have assessed the effectiveness of ginkgo biloba extract in the treatment of cerebral insufficiency, which is a syndrome combining mild cognitive impairment, headaches, confusion, poor concentration, fatigue, and dizziness, and is associated with mood disorders. Long-term treatment with ginkgo biloba extract at 120–150 mg/day reduced symptoms and improved short-term memory [169; 170].

Some evidence supports the effectiveness of ginkgo biloba extract in the treatment of peripheral vascular disorders, including intermittent claudication and, to a lesser degree, Raynaud syndrome [33; 171]. In fact, one clinical trial demonstrated that ginkgo biloba extract is as effective as pentoxifylline, the standard medication for the treatment of intermittent claudication [172]. Despite its ability to improve circulation, multiple clinical trials failed to show the efficacy of ginkgo biloba extract in the treatment of Raynaud disease compared with conventional therapy or placebo [173; 174]. One analysis concluded that while ginkgo biloba treatment did slightly increase treadmill walking time of participants with peripheral artery disease and led to a slight reduction of pain, the therapy produced only modest overall improvements [175].

The beneficial effects of ginkgo biloba extract in a variety of medical conditions, such as tinnitus, cochlear disorders, and vascular retinopathies (including macular degeneration), have also been reported in the scientific literature, although larger studies are required to confirm the clinical outcome. It is possible that in these conditions, ginkgo biloba extract is the most effective when administered in conjunction with standard therapies.

Adverse Effects and Drug Interactions

What is true regarding the safety and tolerability of ginkgo biloba?

Consistently, ginkgo biloba extract is considered a safe and well-tolerated drug when used at the recommended dose for periods of up to six months. In most clinical studies, the incidence of adverse effects is similar to placebo. Less than 2% of patients develop side effects, namely headache, nausea, or mild gastrointestinal symptoms [51]. Two cases of subarachnoid bleeding have been reported in patients taking ginkgo biloba extract and warfarin, and one case of subarachnoid bleeding and intraocular hemorrhage has also been reported in a patient taking ginkgo biloba extract and acetylsalicylic acid concurrently. A case of postoperative bleeding has also been reported after laparoscopic surgery [176]. In these cases, however, the

causal relationship between ginkgo biloba extract and bleeding was not clearly established. Furthermore, bleeding was not reported in any of the clinical trials involving hundreds of thousands of subjects [51]. Nonetheless, it is advisable to discontinue ginkgo biloba extract administration several days prior to surgery [82].

Toxicology

Although in vivo studies did not report either embryotoxic or teratogenic effects of ginkgo biloba extract, this phytomedicine should be avoided during pregnancy and breastfeeding [33; 82; 177]. As mentioned, severe contact dermatitis, similar to that caused by poison ivy, can result from direct contact with the pulp of ginkgo fruit of the female tree. Ingestion of ginkgo seeds, but not leaves, in large amounts (50 or more) causes headache, nausea, diarrhea, and even seizures. This condition is known in Japan as *gin-nan* [82; 147]. Pollen from the male tree can be allergenic for sensitive individuals [51].

Dosage

Standardized extracts are administered at a daily dose of 120–240 mg, in two or three equal doses, for periods of six months or longer [33; 82; 157; 158].

GINSENG

Efficacy: **★E**

Safety: **No S data**

Common Name and Scientific Name

Ginseng is a designation that applies to an HM that is prepared from the root of different plants of the Araliaceae family. Asian ginseng is obtained from *Panax ginseng,* American or Canadian from *P. quinquefolius*, and Japanese from *P. japonicus*. Siberian (Russian) ginseng is obtained from the root of *Eleutherococcus senticosus*, a plant that, although a member of the same Araliaceae family, is not a member of the *Panax* genus and, hence, is not considered a true ginseng. High-quality ginseng root is harvested in the autumn from plants that are 5 to 6 years old.

Historical and Current Use

What are the most important bioactive compounds in ginseng?

The name *Panax* is derived from the Greek *panacea*, meaning cure-all. True to its etymology, the root of the plant has been historically used for a variety of purposes, such as improvement of cognitive and physical performance (i.e., ergogenic effect), cardiovascular diseases (e.g., hypertension), diabetes, cancer, immunomodulation, and menopause. Evidence-based knowledge regarding ginseng's medicinal properties is limited and has generally failed to support historical claims, possibly with the exception of clinical trials assessing the hypoglycemic properties of ginseng [33; 178; 179; 180; 181; 182].

Pharmacology

Several chemicals, including polysaccharides (e.g., ginsan, ginsenans) and a variety of saponins known as ginsenosides, are found in ginseng [82]. Ginsenosides, the most important bioactive compounds, are complex molecules with a steroidal skeleton and modified side chains. The concentration of different ginsenosides varies among species, age of plant, and season of harvest and contributes to the limited understanding of the pharmacologic and physiologic properties of each compound [82]. Adulterants are commonly found in ginseng preparations due to the high cost of authentic ginseng roots, and the presence of natural methylxanthines also may contribute to some reported physiologic effects [82].

Ginsenosides Rb1, Rg1, and Rg2 improve cognitive performance, a mechanism likely related to the stimulation of cholinergic activity implicated in the mechanisms of learning and memory [82; 183; 184]. Both in vitro and in vivo models of Parkinson disease have shown that ginseng extracts have a neuroprotective effect against 1-methyl-1-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in rodents [185]. Gintonin, a novel glycolipoprotein, is a ginseng derivative found in the root of Korean ginseng [186]. Gintonin holds lysophosphatidic acid (LPA), a serum phospholipid that stimulates cell proliferation, migration, and survival [186; 187; 188]. It is thought that gintonin causes significant elevations in levels of intracellular calcium that promote calcium-mediated cellular effects. Research suggests that gintonin has antioxidant and anti-inflammatory effects against different models of neurodegeneration [186; 187; 189]. In studies of neurodegenerative diseases, such as Alzheimer disease and Parkinson disease, gintonin has demonstrated neuroprotective activity by providing action against apoptosis- and oxidative stress-mediated neurodegeneration [186; 187; 189]. In vitro and in vivo studies have demonstrated that ginseng polysaccharide GH1 and ginsenosides Rb2 and Re effectively reduce hyperglycemia and liver glycogen in genetically obese mice as well as in patients with and without type 2 diabetes [178; 190; 191]. Ginseng also stimulates insulin synthesis and release, an effect possibly caused by the increase in nitric oxide production by ginseng [192]. Preliminary results suggest that ginseng also regulates intestinal absorption of glucose and glycosylation of hemoglobin A1c (HbA1c) [179]. A variety of studies (human, animal, cell) have shown that different processed ginseng extracts and specific ginsenosides possess beneficial effects on type 2 diabetes. Most studies of individual ginsenosides have focused on Rb1, Re, or Rg1 as these are the main components of ginseng and easily obtained. However, their large molecule structure results in poor systemic bioavailability. It is thought that these large-molecule ginsenosides may be a form of storage for saponins in ginseng plants rather than the active form in vivo. The smaller molecule ginsenosides (Rg3, Rh1) may be the ingredient that exerts therapeutic effects [193; 194; 195].

In vitro studies have shown that ginsenosides cause vasodilation and lower blood pressure and that panaxynol, a potent inhibitor of thromboxane A2, prevents platelet aggregation [196; 197]. However, further scientific evidence of the antihypertensive effects of ginseng is required prior to considering its potential benefits in cardiovascular diseases. One double-blind controlled trial found that ginseng significantly improved arterial stiffness and systolic blood pressure but had no noted effect on diastolic blood pressure [198]. Research challenges to understanding the potential benefits of ginseng in cardiovascular disease include understanding and identifying the distinct cardiovascular properties of the different ginsenoside compositions, identifying what likely are multifaceted mechanisms that account for the effects of the distinct compositions, and determining which ginsenosides mediate which cardiovascular properties [199].The immunostimulatory and antiproliferative properties of ginseng have also been reported in the scientific literature, but further studies are required [200]. Ginseng has been studied for use in the treatment of menopause symptoms, due to the steroid-like chemical composition of ginsenosides, but the results were inconclusive.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Society for Integrative Oncology recommends 2,000 mg daily of encapsulated American ginseng root powder can be considered to improve fatigue during chemotherapy and radiation for breast cancer.

(https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21397. Last accessed June 10, 2022.)

Level of Evidence: C (Recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.)

Evidence-Based Therapeutic Use and Effectiveness

A Cochrane Review has concluded that the beneficial effects of ginseng preparations were "not established beyond reasonable doubt" [184]. Other literature reviews, however, have reported that ginseng extracts effectively reduced blood glucose levels in patients with type 2 diabetes, although information regarding dosage and long-term effects is still incomplete [33; 179; 201]. A modest improvement in cognitive performance has also been reported [33; 179]. Ginseng is also being investigated for use in the treatment of chronic fatigue, respiratory tract infections, stroke, dermatologic diseases, and as an adjuvant to chemotherapy in the treatment of non-small-cell lung cancer [202; 203; 204; 205; 206; 207; 208].

Adverse Effects and Drug Interactions

Ginseng preparations are generally well tolerated when administered within the recommended dosage, and the available animal and human studies suggest that it is safe [82]. As a result of its hypoglycemic properties, it should be used cautiously in patients with type 2 diabetes concurrently treated with oral hypoglycemic drugs. Improvements in blood glucose measures and glycemic control with ginseng use have been inconsistently reported [82].

Anticoagulant properties may also account for a few reports of epistaxis and vaginal bleeding. In contrast, a randomized, controlled clinical trial has shown that ginseng increases the risk of blood clotting in patients treated with warfarin. This pharmacokinetic interaction occurs only after long-term administration of ginseng and results from the induction of hepatic CYP450 isoforms responsible for warfarin metabolism [209].

Interactions between ginseng and MAO inhibitors have also been reported and may cause headaches, insomnia, nervousness, and mood disorders. Pharmacokinetic (e.g., CYP450 induction) and pharmacodynamic potentiation of antihypertensive drugs have also been reported, and it should not be administered to hypertensive patients [33; 82].

A few case reports describe the occurrence of diarrhea, unstable mood, skin rash, or itching after long-term administration. Ginseng has also been associated with loss of menstrual periods and vaginal bleeding in menopausal women. Therefore, ginseng should not be administered to patients with hormone-sensitive conditions, such as breast or uterine cancer and endometriosis [82]. In men, it may be associated with estrogen-like effects, such as reduced libido and gynecomastia [33].

Toxicology

At normal doses, ginseng is reported in the literature as being safe. Nevertheless, ginseng should be avoided during pregnancy and breastfeeding [33; 82; 137]. A case of reversible masculinization of a newborn girl when a mother allegedly took *Eleutherococcus senticosus* (Siberian ginseng) during pregnancy has been reported [210]. In fact, it resulted from the adulteration of the original product and substitution of *Periploca sepium*, a vine of the milkweed family, for ginseng. *Periploca sepium* has been used in traditional Chinese medicine for its stimulatory and libido enhancing effects. Accordingly, it should be emphasized that the mentioned report has been erroneously used as published evidence of ginseng toxicity [211; 212]. Pediatric safety concerns regarding ginseng treatment for upper respiratory tract infections were addressed in a 2008 Canadian trial involving 75 subjects (3 to 12 years of age) given standard doses, low doses, or placebo. The treatments were well tolerated, considered safe, and warrant additional research for use on these and other types of pediatric infections [213].

Dosage

Purified ginseng extracts are generally standardized to 4% or 7% ginsenoside contents. Usually, 100–200 mg of standardized 4% extract is administered orally once or twice daily, for as many as 12 weeks [82]. In traditional Chinese medicine, 0.5–2 g/day of dried ginseng root, equivalent to 200–600 mg of standardized extract, is commonly used. Long-term administration of ginseng should not exceed 1 g/day of the dry root form or 400 mg/day in the extract form. It is administered daily for two to three weeks, then discontinued for one to two weeks. This treatment schedule may be repeated for several months [33; 137].

ECHINACEA

Efficacy: ★★**E**

Safety: **S**

Common Name and Scientific Name

The designation echinacea applies to several plants of the Asteraceae/Compositae family, including *E. angustifolia*, *E. pallida*, and *E. purpurea*. Echinacea, also known as coneflower, narrow-leafed cone-flower, or black-eyed Susan, is indigenous to North America. It adapts well and thrives in temperate climates, including Europe and Asia, where it has been planted for decorative and medicinal purposes.

Historical and Current Use

Echinacea was used by Native Americans for a wide variety of conditions, including chewing the roots for toothaches and gingivitis, root and leaf infusion for stomach pain, colds, and infections, and topically as a disinfectant and for wound healing. The use of echinacea was quickly adopted by early European settlers, and shortly thereafter, it became widely used by European herbalists and physicians. In Germany, it has been commonly used in mainstream medicine for almost a century. The German Commission E has approved the use of echinacea for the amelioration of common-cold symptoms, upper respiratory infections, and urinary tract infections, as well as topical administration for treatment of superficial wounds [214]. The scientific literature generally supports a beneficial effect of echinacea extracts in the treatment of cold symptoms, but evidence of its efficacy in the prevention of colds is still limited [215; 216]. Echinacea is the most widely sold HM in the United States and is the third most popular natural product overall (surpassed only by fish oil and glucosamine) [10].

Pharmacology

Preparations from different portions (e.g., root, leaves) of the echinacea plants (e.g., *E. angustifolia*, *E. purpurea*, *E. pallida*) are collected during the blooming season. The products are usually dried, and several chemical components, namely caffeic acid derivatives (e.g., echinacosides, cichoric acid derivatives), flavonoids (e.g., quercetin), alkylamides, and polysaccharides, are identified upon alcoholic extraction [51]. Laboratory analysis of echinacea extracts with high-pressure liquid chromatography provides the chemical fingerprint of different echinacea species. In fact, in *E. purpurea*, no echinacosides are detected, whereas they are abundant in *E. angustifolia* and *E. pallida*. On the other hand, the amount of cichoric acid present in *E. purpurea* is 40- to 60-fold higher than that present in *E. angustifolia* and *E. pallida*, respectively [217]. The relative concentration of various chemicals within the same species also varies in different plant parts. Echinacoside concentrations are higher in the root, whereas cichoric acid concentrations are higher in the flower of all echinacea species than in other plant parts.

Due to its complex chemical makeup, the precise pharmacologic and therapeutic properties of each compound remain to be determined. Naturally occurring phenols, such as the caffeic acid derivatives, are potent antioxidants due to the presence of hydroxyl groups on aromatic rings that scavenge tissue-damaging free radicals [217]. In vitro experiments revealed that alkylamides from echinacea inhibit cyclooxygenase and 5-lypoxygenase, accounting for its anti-inflammatory properties [218; 219].

The immunostimulatory properties of echinacea have been demonstrated both in vitro and in vivo. Nonspecific effects, such as macrophage proliferation, stimulation of interleukin-1, tumor necrosis factor, and interferon stimulation, as well as specific effects, such as increase in numbers of T lymphocytes and natural killer cells, have been reported in several studies [33]. Because the total immunostimulatory effect of echinacea in humans remains to be established, the German Commission E discourages the use of echinacea in patients with autoimmune diseases.

Many preparations are standardized to 4% to 5% echinacosides, while others also report the concentration of cichoric acid. A detailed study conducted by investigators from the University of Colorado Health Sciences Center analyzed 59 samples of echinacea-only preparations purchased from 11 retail outlets in the Denver area [220]. Ten percent of the samples did not contain measurable amounts of echinacea, and the species content only agreed with the label in 52% of the cases. Twenty-one preparations claimed to be standardized, but only nine met the composition reported on the label. Although the efficacy of echinacea in the treatment of some medical conditions has been reasonably established, the lack of species identification and standardization, as well as product contamination/adulteration, should be thoroughly investigated prior to being administered. The poor quality of many available products certainly contributes to, or may account for, the conflicting results and significant number of negative reports published in the scientific journals.

Evidence-Based Therapeutic Use and Effectiveness

The therapeutic effectiveness of echinacea preparations in prevention and treatment of the common cold has been extensively studied. Several extensive reviews and meta-analysis studies have been published, and some have provided conflicting or inconclusive results.

Researchers evaluated the therapeutic effectiveness of echinacea in the treatment of the common cold based on nine placebo-controlled clinical trials and concluded that its effectiveness has not been established [221].

Three randomized, double-blind, and placebo-controlled trials assessed the effectiveness of echinacea on the avoidance of and severity of colds. Consistently, they all revealed that subjects preventively treated with standardized echinacea extracts acquired fewer colds (22%, 58%, 49%) than the placebo group (33%, 82%, 56%) [222; 223; 224]. However, due to the small number of subjects studied in each trial, the decreases were not statistically significant. A meta-analysis evaluated these three clinical trials, and due to the common methodology used, the results of almost 400 subjects were combined [215]. The meta-analysis suggests that the risk of developing a cold was 55% higher in the placebo than in the echinacea-treated group, a statistically significant difference.

A 2014 Cochrane review also evaluated the effects of echinacea on naturally acquired colds [225]. Twenty-four published trials met their inclusion criteria. In the treatment of colds, echinacea was not effective in most clinical trials and beneficial or marginally better than the placebo group in only one trial. In the 12 prevention clinical trials, no significant difference was observed between echinacea and placebo groups, but a later analysis found a 10% to 20% reduction in cold risk [225]. Interestingly, the authors also commented on the pervasive issue of lack of standardization, the variability in bioactive composition of echinacea preparations, and the likelihood that they may contribute to, or account for, the lack of consistency in treatment and prevention outcomes.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Institute for Clinical Systems Improvement, the evidence on the efficacy of *Echinacea* for the prevention of viral upper-respiratory infection is limited. The studies are either small or of low quality, or the evidence is insufficient to make conclusions. More studies are needed.

(https://www.icsi.org/wp-content/uploads/2019/01/RespIllness.pdf. Last accessed June 10, 2022.)

Level of Evidence: Expert opinion

In vitro and in vivo studies, and in some cases preliminary clinical evidence as well, support other possible therapeutic applications of echinacea preparations (e.g., immunostimulant, anti-infective, wound-healing) [82]. However, due to the limited data, the actual therapeutic outcome is inconclusive.

Adverse Effects and Drug Interactions

In clinical trials, echinacea preparations are generally well tolerated, and the number of patients dropping out of studies is similar to the placebo group. A single study conducted in children 2 to 11 years of age reported the occurrence of an allergic rash [226]. In adults, one review found that the most common adverse effects were nausea and vomiting (<1%), abdominal pain (<1%), and mild drowsiness and headache (<1%) [33]. One case of anaphylaxis has been reported in a patient with a history of atopic reactions [227]. Echinacea should not be administered to individuals with allergies to other plants of the Asteraceae family, including daisies, ragweed, marigolds, and chrysanthemums. It is also recommended to avoid echinacea if currently on immunosuppressants [82].

Toxicology

Both in vitro and in vivo studies suggest that, even when administered at doses several-fold higher than the ones normally used, echinacea is devoid of toxicity. Analysis of 112 pregnant women who were exposed to echinacea preparations during the first trimester of pregnancy showed no difference in fetal health when compared with the nonechinacea-exposed group [228]. Although other studies seem to confirm safety, echinacea preparations should be avoided during the first trimester due to lack of definitive evidence.

Dosage

For treatment of cold symptoms and upper respiratory infections, an initial 300–1,000 mg titrated dose of powdered herb in capsules or its equivalent (tincture or juice) is administered for five to seven days [33; 51; 137; 179]. Use for more than eight weeks at a time should be avoided because of the potential for immunosuppression [82]. Preparations containing 15% pressed herb are used topically as disinfectants.

KAVA

Efficacy: ★★★E

Safety: **AEs/DIs/UnS**

Common Name and Scientific Name

Kava (*Piper methysticum*), a member of the pepper family, is a widely cultivated shrub indigenous to the South Pacific islands. It is also known as kava-kava, kawa, or ava pepper [82].

Historical and Current Use

A drink prepared from the root of the kava plant has been used traditionally in the South Pacific for ceremonial, social, and medicinal purposes for several centuries, if not millennia. It

is used for its mild relaxing and calming properties, culturally comparable to alcohol use in Western societies. Following the European trend, the use of kava for the treatment of anxiety has become popular in the United States. In some countries, including Germany, it has been commonly prescribed to treat anxiety, stress, and insomnia, although very serious concerns regarding potential hepatotoxicity have led to warnings and bans in North America.

Pharmacology

The lipid-soluble extract of kava is rich in kava pyrones, including kavain, dihydrokavain, and methysticum [82; 229]. Kava pyrones block voltage-dependent sodium channels, a mechanism responsible for the local anesthetic properties of kava drinks, which causes numbness and tingling of the mouth. Kava also contains antioxidant flavonoids and alkaloids. It has been reported that kava has a direct effect on limbic structures, particularly the amygdala. It does not bind to the gamma-aminobutyric acid $(GABA)_A$ receptors, unlike benzodiazepines, which target the $GABA_A$ receptors abundantly distributed in the cerebral cortex. This may account for the difference in anxiolytic properties of kava, which, unlike benzodiazepines, does not cause sedation [230].

At higher doses, kava lactones also have muscle-relaxant and anticonvulsant properties, which are possibly related to the stimulation of the glycine receptor [231]. Kavain has dose-dependent antiplatelet aggregation and anti-inflammatory properties [232].

Evidence-Based Therapeutic Use and Effectiveness

The clinical effectiveness of kava has been widely studied, and clinical studies strongly support its efficacy in the treatment of moderate and mild cases of anxiety. One meta-analysis included data from 11 double-blind, controlled clinical trials, and the authors concluded that kava, when compared with placebo, is effective in the symptomatic treatment of anxiety [233]. A standardized preparation of kava (LI 150) was as effective as the anxiolytic drugs buspirone and opipramol [234; 235]. An extensive literature review also confirmed the clinical effectiveness of kava preparations in the treatment of anxiety [33].

Several clinical studies assessed the effect of kava on memory and compared it with both the anxiolytic oxazepam and placebo [230]. The studies concluded that kava, unlike oxazepam, does not impair cognitive performance and memory. In fact, an improvement in memory was observed in the kava-treated group, but these interesting results wait for confirmation [33; 236]. A review of at least 10 studies on the effects of kava on cognition have been published, but the heterogeneity of dosages/potency and preparations used precludes meta-analysis. At higher dosages, reaction time may be impaired [237; 238; 239]. Kava has been promoted for use in attention deficit hyperactivity disorder; however, clinical trials are lacking and such use is not recommended [239; 240].

EVIDENCE-BASED PRACTICE RECOMMENDATION

A Cochrane Review found that, compared with placebo, kava extract is an effective symptomatic treatment for anxiety, although, at present, the size of the effect seems small. The effect lacks robustness and is based on a relatively small sample. The data available from the reviewed studies suggest that kava is relatively safe for short-term treatment (1 to 24 weeks), although more information is required.

(https://www.cochrane.org/CD003383/DEPRESSN_kava-extract-for-treating-anxiety. Last accessed June 10, 2022.)

Level of Evidence: Meta-analysis

Adverse Effects and Drug Interactions

What are possible adverse effects of kava use?

In clinical trials, the side effects of kava preparations were rare and mild, with gastrointestinal discomfort, restlessness, headache, and dizziness reported in about 2% of patients. Kava dermatitis, a yellow discoloration of the skin accompanied by scaly dermatitis, is only observed in chronic heavy kava drinkers and reverses after discontinuation of kava administration. This skin condition resembles pellagra but is resistant to niacin treatment [82]. Neurotoxicity, pulmonary hypertension, and choreoathetosis have also been reported in chronic heavy drinkers in the Australian Aboriginal population [241]. A few rare cases of kava-induced Parkinson-like extrapyramidal disorders have been reported, as well as the aggravation of existing Parkinson disease in one patient and one case in the United States of rhabdomyolysis related to the ingestion of a large amount of kava [51; 235]. There are some reports suggesting that kava may cause severe and, in some cases, irreversible liver damage. As a result, the FDA issued an advisory letter to healthcare professionals stating possible health risks [242].

Kava extracts interact with and potentiate the effects of anxiolytic and depressant drugs, such as benzodiazepines, barbiturates, and alcohol. Due to its antiplatelet properties, kavain-containing preparations should not be administered to patients undergoing anticoagulant therapy, although the clinical relevance of this potential interaction has not been established. Kava preparations should also be avoided in patients with extrapyramidal disorders, including Parkinson disease. Finally, due to the potential hepatotoxicity, kava should not be administered to patients with liver disease or those treated with potentially hepatotoxic medications such as acetaminophen, anabolic steroids, or the anticancer agent methotrexate [33; 82; 243]. As a precautionary measure, kava should not be administered during pregnancy and lactation due to the lack of safety studies [82]. Kava administration should be discontinued at least 24 hours prior to surgery because of possible potentiation of the sedative effect of anesthetics [244].

Toxicology

More than 30 cases of kava-induced hepatotoxicity, ranging from hepatitis and cirrhosis to acute liver failure and death, have been reported in the literature. One study of lipid-extractions of kava led researchers to state that rather than being caused by directly toxic mechanisms, reactions to kava likely stemmed from immunologically mediated idiosyncratic mechanisms; therefore, the hepatotoxicity of kava may be similar to benzodiazepines [245]. An Australian trial concluded that water-extracted kavalactones, using dried roots sourced from the island of Vanuatu and prepared in a controlled pharmaceutical manufacturing facility, caused neither an increase in liver enzymes nor hepatotoxic symptoms [246]. Other studies have shown that kava suppresses CYP450 enzymes in the liver, leading to hepatotoxic concentrations of concurrently administered drugs [82; 247]. Although no cases of hepatotoxicity were reported in any of the clinical trials included in a Cochrane Review, it is not recommended for use in the United States [137; 233].

Dosage

Standardized products are available, and the usual recommended daily dose of kavalactones ranges from 120–250 mg/day, divided in two to three equal doses [33; 51]. In the United States, most formulations are standardized to 30% or 55%, meaning that a 100 mg tablet contains 30 mg or 55 mg of kavalactones, respectively. Usually, kava use should be limited to three months to avoid potential habituation, and patients should be advised of the potential adverse effects on motor coordination and capacity to drive or operate heavy machinery [51].

GARLIC

Efficacy: ★★**E**

Safety: **AEs/DIs**

Common Name and Scientific Name

Garlic (*Allium sativum*), also known as allium, is related to chives (*Allium schoenoprasum*) and onions (*Allium cepa*), and all belong to the Liliaceae family, which also includes lilies.

Historical and Current Use

The recorded medicinal use of garlic goes back to ancient Egyptian, Greek, and Roman civilizations. It was used for the treatment of a variety of conditions, including heart problems, headaches, intestinal parasites, and tumors, and as a local disinfectant. In the nineteenth century, Louis Pasteur also reported the antimicrobial properties of garlic. It is now used for its effectiveness in reducing cholesterol and for its antithrombotic and antioxidant properties, as well as for its ability to lower blood pressure. Together, these properties have also provided some support for the use of garlic in the prevention of cardiovascular diseases, including atherosclerosis [33; 37; 51]. The benefits of garlic in the treatment of certain cancers, specifically stomach and colorectal, have also been investigated [248; 249].

Pharmacology

The beneficial effects of garlic have been related to its sulfur compounds. More than 20 different sulfur compounds have been identified in garlic. The sulfur compound allinin (S-allyl-l-cysteine sulfoxide) is transformed to allicin (diallyl thiosulfinate) via the enzyme alliinase when the bulb is crushed or ground. Allicin is an unstable molecule that is converted into more stable compounds. Other sulfur compounds, such as peptides, steroids, terpenoids, flavonoids, and phenols, derive from allicin metabolism and have been the subject of investigations aimed at identifying their biologic role [250]. In vitro and in vivo studies have associated allicin with the antibacterial properties of garlic. Commercially available garlic extracts are standardized to the allicin content. Three water-soluble allicin derivatives, s-allylcysteine (SAC), s-ethylcysteine (SEC), and s-propylcysteine (SPC), are the most effective in reducing in vitro cholesterol synthesis in hepatocytes by 42% to 55% [251].

Methyl-allyl trisulfide (MATS), a lipid-soluble allicin derivative, inhibits cyclooxygenase activity and prostaglandin synthesis and is responsible for the antithrombotic and antiplatelet aggregation properties of garlic [252]. Another sulfur compound, diallyl trisulfide (DATS), is a potent inhibitor of colon and lung human cancer cell proliferation in cell cultures and is at least partially responsible for the anticancer properties of garlic [253; 254; 255; 256].

The antioxidative properties of garlic are exerted indirectly through the sulfur compound-induced stimulation of protective antioxidant enzymes present in the body, including glutathione-S-transferase, superoxide dismutase, and catalase [37; 252].

Evidence-Based Therapeutic Use and Effectiveness

Several clinical trials have reported that garlic lowers total cholesterol levels by 8% to 15% [257; 258]. This effect results from the lowering of the low-density lipoprotein (LDL) and triglycerides, while the high-density lipoprotein (HDL) values remain unchanged. A meta-analysis confirmed that, after 10 to 12 weeks, garlic lowers plasma cholesterol, although the benefits (4% to 6%) were less pronounced than previously reported, and this effect was not statistically significant after a six-month period [259]. In 2001, an extensive meta-analysis of 34 randomized clinical trials including almost 2,000 patients confirmed the previous assertions [260]. A meta-analysis of 26 studies found that, overall, garlic is superior to placebo in reducing serum total cholesterol and triglyceride levels

[261]. Compared with placebo, serum total cholesterol and triglyceride levels in the garlic group were reduced by 0.28 mmol and 0.13 mmol, respectively. Garlic powder and aged garlic extract were more effective in reducing serum total cholesterol levels; garlic oil was more effective in lowering serum triglyceride levels. Garlic did not lower LDL cholesterol, HDL cholesterol, apolipoprotein B, or the total cholesterol/HDL ratio [261]. Results of a 2018 meta-analysis found that garlic can reduce total cholesterol and LDL levels, but not HDL and total triglyceride levels [262]. In conclusion, garlic preparations are moderately effective in lowering LDL and triglycerides and do not change the HDL concentration in the plasma [33].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Physicians, the American College of Cardiology Foundation, the American Heart Association, the American Association for Thoracic Surgery, the Preventive Cardiovascular Nurses Association, and the Society of Thoracic Surgeons recommend that treatment with garlic should not be used with the intent of reducing cardiovascular risk or improving clinical outcomes in patients with stable ischemic heart disease.

(http://www.onlinejacc.org/content/64/18/1929. Last accessed June 10, 2022.)

Strength of Recommendation: Strong

The effects of garlic on blood pressure have been studied in several clinical trials. Some studies have shown a small (6%) yet statistically significant effect, although these findings were not replicated by other studies [33]. Garlic is not recommended for the management of hypertension [82; 263].

Garlic has also been shown to inhibit platelet aggregation, as expected by its inhibitory effects on cyclooxygenase and prostaglandin synthesis. The effective dosages are not well established, and comparison with other antiplatelet aggregation drugs is not yet available. Because several reports have associated garlic with bleeding accidents, administration should be limited to lower dosages and co-administration with drugs that affect hemostasis, including antiplatelet aggregation drugs (e.g., aspirin) or anticoagulants (e.g., warfarin), should be avoided [33; 144].

Some clinical studies suggest that garlic preparations slow the progression of atherosclerotic plaques [264]. Although encouraging, these results are preliminary and further studies are required [82].

The anticancer properties of garlic compounds have been reported both in vitro and in vivo, but their clinical effectiveness remains to be established [265]. One small trial in mice showed that garlic extract inhibits growth of certain cancer cells, particularly multiple myeloma. Researchers indicated that the reduced proliferation of cancer cells is at least partly mediated by increased endoplasmic reticulum stress [265]. Another small trial with mice indicated that anticancer properties of garlic are more effective when introduced directly to the cancer cells by injection rather than via oral ingestion [266]. Epidemiologic studies suggest that regular consumption of garlic may be associated with a lower risk of developing gastric and colorectal malignancies [267]. A review of 14 studies of the anticancer properties of garlic and onion supports this association [249]. While the results of one systematic review and meta-analysis suggest a significant inverse correlation between the intake of garlic and the risk of gastric cancer, an analysis of health claims provided to the FDA found no credible evidence supporting the use of garlic for prevention of gastric cancer or breast, lung, or endometrial cancers [261; 268]. Although the epidemiologic evidence is cautiously positive, well-designed clinical trials are needed before a conclusion can be reached [269].

Adverse Effects and Drug Interactions

For patients taking garlic, the highest risk of an interaction is with which drug class?

The most common adverse effects reported are bad breath and body odor [82]. Less commonly, dyspepsia and flatulence are also reported. In rare cases, dermatitis and respiratory difficulty can occur in hypersensitive patients [51]. The highest risk of herb-drug interaction is between garlic and anticoagulant drugs, such as the vitamin K inhibitor warfarin, and antiplatelet aggregation agents, such as ticlopidine and clopidogrel, and results from the pharmacodynamic potentiation of mechanisms of action [144].

Toxicology

Garlic preparations administered within the recommended dosages are safe, although they should not be administered to patients allergic to garlic or to other members of the Liliaceae family, namely chives, onions, leek, or lilies [33; 82; 144]. A dangerous pharmacokinetic interaction between garlic and the protease inhibitor saquinavir has been reported, as it reduces the plasma concentration of the anti-HIV drug by 50% [270].

Dosage

Administration of garlic preparations varies greatly according to the preparation used (i.e., fresh, powder, oil extracts). Standardized preparations to 1.3% allinin or 0.6% allicin are usually administered at 600–900 mg per day. This is considered equivalent to one small clove of fresh garlic [51].

VALERIAN

Efficacy: ★★E

Safety: S

Common Name and Scientific Name

Valerian (*Valeria officinalis*), also known as baldrian, is a member of the Valerianaceae family. Other species of the same family that are also used for medicinal purposes include *V. wallichi* and *V. sambucifolia*.

Historical and Current Use

Historical documents from ancient Greece, China, and India widely report the use of preparations from valerian root and rhizome in the treatment of insomnia and anxiety. This herb, native to Asia and Europe, is found throughout the world. Topically, it has been used in the treatment of acne and wound healing. It has also been used traditionally for the treatment of a variety of disorders, including digestive problems, flatulence, congestive heart failure, urinary tract disorders, and angina pectoris. For the past 200 years, valerian has been widely used in Europe and North America for its mild sedative properties [37; 51].

Pharmacology

A large number of chemicals, including monoterpenes, sesquiterpenes, valepotriates, amino acids, and alkaloids, have been extracted from valerian. Although no single component has been shown to account for its pharmacologic properties, the biologically active valerenic acid has been used as the constituent for standardization. In vivo studies have confirmed the sedative, anxiolytic, and anticonvulsant properties of valerian preparations. Studies have also shown the agonistic effect of valerian and some of its individual compounds on the $GABA_A$ receptors and on the 5-HT5a serotonin receptors [271; 272; 273]. Other studies have revealed that valerian extracts inhibit the presynaptic GABA carrier, further contributing to an increased GABAergic inhibitory activity in the brain [274]. Valerenic acid also inhibits GABA transaminase, the enzyme responsible for GABA metabolism [275]. Together, these findings contribute to a better understanding of the molecular mechanisms underlying the sedative and anticonvulsant properties of valerian. More recently, research has identified valerenic acid and its modulation of the $GABA_A$-ergic system as probable cause of the anxiolytic effects, a mechanism similar to benzodiazepines (e.g., diazepam) [276]. In addition to valerenic acid, isovaleric acid, didrovaltrate, borneol, and some lignans have also been proposed to contribute to the anxiolytic effect of the plant [277].

Evidence-Based Therapeutic Use and Effectiveness

A systematic review of nine randomized clinical trials found that results regarding the effectiveness of valerian in the treatment of insomnia were inconclusive [278]. Some benefits were reported within one to two days, but benefits on sleep were observed only after four weeks of treatment. A larger European clinical trial reported that the valerian had minimal or no effect on sleep regulation [279]. Unfortunately, patients were treated for only two weeks, a time period considered too short when compared with previous studies, which may account for the negative outcome. A 2011 systematic review of CAM practices on insomnia reached a similar conclusion as the European clinical trial regarding valerian [280]. The American Academy of Sleep Medicine suggests that valerian not be used for sleep-onset or sleep-maintenance insomnia as the benefits are considered to be approximately equal to the risks [281].

No well-designed trials of valerian in the treatment of anxiety in humans have been published to date. An investigation of the effect of valerenic acid on rats concluded that valerian use was related to a reduction of anxious behavior, and a small-scale study found that valerenic acid was effective for reducing anxiety before a medical procedure [276; 282].

Adverse Effects and Drug Interactions

In clinical trials, valerian side effects were minor, most commonly headache, stomach upset, or dizziness, and were usually reported as frequently as in the placebo group. Adverse effects on reaction time and alertness were much lower than benzodiazepines. Dependence and withdrawal have not been reported in any of the clinical trials, although a single case report of withdrawal symptoms after discontinuation has been published [283]. As valerian and benzodiazepines similarly target the $GABA_A$ receptor, it is possible that the patient may develop physical dependence after lengthy administration. It is therefore advisable to discontinue valerian administration progressively. Valerian potentiates the effects of other sedatives, such as benzodiazepines, barbiturates, alcohol, kava, and chamomile, and should not be co-administered in conjunction with these drugs or phytomedicines [33].

Toxicology

Valerian is considered safe by the FDA, but administration during pregnancy and breastfeeding is not advised due to the limited availability of safety data [82].

Dosage

In clinical trials, for the treatment of insomnia, 900 mg of a standardized solution equivalent or 1.5–3 grams of dried root was administered 30 minutes to 1 hour before bedtime [51]. Valerian extract, in doses of 400–600 mg, has been used in clinical trials evaluating valerian in insomnia [284; 285].

ANDROGRAPHIS

Efficacy: ★★E

Safety: **AEs/DIs**

Common Name and Scientific Name

Andrographis (*Andrographis paniculata*) is also known as *Justicia paniculata*, green chiretta, king of bitters, kan jang, and sambiloto. It is an herb naturally found in Asia, including India, Southeast Asia, and southern China, and it is also cultivated for commercial use in the preparation of traditional HMs. Andrographis is an annual tall herb, up to one meter high, with small white flowers. It thrives in humid climates and shady areas.

Historical and Current Use

The bitter-tasting leaves of andrographis have been used for centuries in traditional Indian and Chinese medicine in the preparation of an infusion used for the treatment of digestive ailments and fever. In Malaysia, andrographis has also been traditionally used for the treatment of hypertension [286]. In northern European countries, andrographis is used for the prevention of upper respiratory tract infections [33].

Pharmacology

Andrographis is rich in diterpenoids and flavonoids. At least nine diterpenoids, including andrographolide, 14-deoxyandrographolide (DA), and 14-deoxy-11-oxoandrographolide (DDA), have been isolated.

In vitro studies revealed that andrographolide has anti-inflammatory, antiapoptotic, and immunomodulatory properties. In vivo studies demonstrated that both DA and DDA effectively lower blood pressure, decrease heart rate, and cause vasodilation [287]. DA and DDA block calcium channels, increase nitric oxide synthesis, and inhibit ß-adrenergic receptors. All of these actions provide the mechanistic explanation for the hypotensive properties of andrographis [287].

Evidence-Based Therapeutic Use and Effectiveness

Several clinical trials, including almost 900 subjects, have assessed the effectiveness of andrographis in the treatment and prevention of upper respiratory tract infection. Two meta-analyses concluded that andrographis was significantly more effective than placebo for the treatment of upper respiratory tract infection symptoms [288; 289]. A 2017 systematic review and meta-analysis also found that andrographis (*A. paniculata*) improved overall symptoms of upper respiratory tract infection compared to placebo, usual care, or other herbal therapies. Andrographis also shortened the time to symptom resolution [290]. Limited evidence also suggests that andrographis preparations may be effective in the prevention of upper respiratory tract infection [291; 292]. Two clinical studies concluded that andrographis is also effective in the treatment of influenza symptoms, although larger and better-designed studies are needed to confirm the results [33].

One randomized controlled trial of 60 patients with mild hypertriglyceridemia found that *A. paniculate* extract reduced triglyceride levels comparable to the effect of 300 mg/day of gemfibrozil, an LDL-lowering agent [293].

Adverse Effects and Drug Interactions

Andrographis is considered safe and well tolerated. Headache, nausea, vomiting, abdominal discomfort, and nasal congestion are the most commonly reported adverse effects [33; 82]. Although data regarding andrographis interactions with other drugs is still limited, due to andrographis' hypotensive and hypoglycemic properties, concurrent administration with antihypertensive and hypotensive drugs should be avoided.

Toxicology

In clinical trials, a dose-response dependent toxicity of andrographis has been identified, and fatigue, headache, and lymphadenopathy have been described [291; 294; 295]. Three cases of anaphylactic reaction have also been reported [288].

Dosage

Usually, 300 mg of standardized preparations of andrographis (4% andrographolides) is taken four times per day, for as long as two weeks [33].

ENGLISH IVY LEAF

Efficacy: ★★★E

Safety: S

Common Name and Scientific Name

English ivy leaf has traditionally been used in the treatment of what conditions?

English ivy (*Hedera helix*), also known as common ivy, is an evergreen climbing vine. It is native to Europe and Central Asia, grows easily, and is commonly found in humid environments and in forests. It is often used for decorative purposes. It is different from ground ivy (*Glechoma hederacea*) and American ivy (*Parthenocissus quinquefolia*). It is particularly important not to confuse it with poison ivy (*Rhus toxicodendron*).

Historical and Current Use

The glossy and dark green leaves of common ivy have been traditionally used for the treatment of a wide variety of disorders, including respiratory disease, arthritis, fever, burns, and infections. It is now used as an expectorant and in the treatment of bronchitis and asthma [51].

Pharmacology

Ivy leaves are rich in saponins (e.g., hederin, hederacoside) but also contain sterols, flavonol glycosides, and polyalkenes among other chemicals. Saponins stimulate secretion of mucus in the upper respiratory tract and have a mucokinetic and mucolytic effect [229]. They also prevent acetylcholine-induced bronchospasm [296]. Hederacoside C has antifungal and antibacterial properties [214]. Together, these bronchodilatory and antimicrobial properties of ivy leaf extracts provide the pharmacologic evidence to support their beneficial effects in the treatment of upper respiratory tract infections.

Evidence-Based Therapeutic Use and Effectiveness

The clinical efficacy of ivy leaf extracts has been the subject of one meta-analysis [297]. Five clinical trials, three of which measured its effect on children, indicated that the treated group showed an improvement in chronic bronchial asthma. In another study not included in the previous review, 1,350 children with chronic bronchitis were treated with standardized ivy leaf extracts for four weeks. A significant improvement or cure of the following symptoms was observed, when compared with the baseline: cough (92%), expectoration (94%), dyspnea (83%), and respiratory pain (87%) [298]. A postmarketing study of almost 10,000 patients with bronchitis showed that, after a seven-day treatment with ivy leaf extracts, 95% of the patients had improved significantly [299]. One 2021 systematic review found that while ivy leaf preparations are safe for use in cough due to acute upper respiratory tract infections, the effects are minimal at best and of uncertain clinical importance [300].

Adverse Effects and Drug Interactions

Ivy leaf extracts are generally considered safe. Mild adverse effects, such as gastrointestinal discomfort, eructation, or nausea, are observed in 0.2% to 2.1% of patients [298; 299]. No drug interactions have been reported. Considering the detergent-like actions of saponins, it has been suggested that ivy leaf extracts should not be ingested at the same time as other drugs, considering the unlikely possibility that ivy leaf extracts may facilitate the absorption of the other drugs. However, this warning is not supported by any evidence and should be considered as speculative.

Toxicology

Ingestion of ivy berries can be toxic, and falcarinol present in cut ivy leaves may cause contact dermatitis, particularly in sensitive individuals [144]. In a bizarre case, ingestion of ivy leaves caused mechanical obstruction and suffocation [301]. Toxicology tests confirmed the cause of death as being suffocation, and no toxin was detected in cardiac blood, femoral blood, or urine of the deceased [301].

It has been suggested that ivy leaf products should be avoided during pregnancy because the emetine content in ivy leaf may cause uterine contractions [302]. Data on the effects of ivy leaf extracts during lactation are not yet available, and as a result, ingestion of ivy leaf extracts in these cases should be avoided.

Dosage

Standardized ivy leaf extracts are available as a hydroalcoholic extract syrup (105 mg/day of dried ivy leaf extract), ethanolic extract drops (35–40 mg/day of dried ivy leaf extract), or suppositories (160 mg/day of dried ivy leaf extract) [297].

PEPPERMINT

Efficacy: ★★**E**

Safety: **S**

Common Name and Scientific Name

Peppermint (*Mentha x piperita L.*) is a hybrid of *Mentha spicata L.* (spearmint) and *Mentha aquatica L.* of the Lamiaceae (mint) family. It is also known as peppermint oil, menthol, mint, balm mint, brandy mint, and green mint. The plant is native to Europe but is widely cultivated in the United States and Canada [82; 303].

Historical and Current Use

Peppermint leaf and peppermint oil have a history of use for digestive orders that dates back to ancient Egypt. The plant was first described in England in 1696, and both the leaf and the oil have been used in Eastern and Western traditional medicine as antispasmodics, aromatics, and antiseptics. Peppermint oil is used in herbal remedies, cosmeceuticals, personal hygiene products, foods, and pharmaceutical products. Topical preparations have traditionally been used to calm pruritus and relieve irritation and inflammation [303; 304; 305; 306; 307]. Peppermint oil is widely used as a spasmolytic agent in irritable bowel syndrome (IBS) [307; 308; 309].

Pharmacology

Peppermint oil is complex and highly variable, with more than 100 components isolated from the oil. Relative concentrations vary depending on climate, cultivar, and geographic location. Peppermint yields 0.1% to 1% of volatile oil composed primarily of menthol (29% to 48%), menthone (20% to 31%), and menthyl acetate (3% to 10%) [82]. Menthol is rapidly absorbed following oral administration, and elimination is mainly via bile [82; 307]. Peppermint oil has a demonstrated dose-related antispasmodic effect on gastrointestinal smooth muscle, attributed to calcium channel blockade [82; 310; 311]. It reduces intragastric pressure, phasic contractility of the proximal stomach, and appetite, with negligible effects on gastric sensitivity, tone, and nutrient tolerance in health [309].

Evidence-Based Therapeutic Use and Effectiveness

Irritable Bowel Syndrome

The clinical effectiveness of peppermint oil in the treatment of IBS has been extensively studied. A Cochrane review of clinical studies that evaluated the efficacy of bulking agents, antispasmodics (e.g., peppermint oil), and antidepressants for the treatment of IBS was published in 2013 [312]. The review included 56 randomized controlled trials published between 1966 and 2009 involving 3,725 patients with IBS who were older than 12 years of age. The primary outcomes evaluated were improvements of abdominal pain, global assessment, and symptom score. Both antidepressants and antispasmodics demonstrated improvement in outcome measures. Abdominal pain improved in 58% of antispasmodic patients compared with 46% with placebo. Global assessment showed 57% improvement in patients taking antispasmodics compared with 39% with placebo; and 37% of patients taking antispasmodics showed improved symptom score compared with 22% with placebo [313]. A subgroup analysis of different types of antispasmodics, including peppermint oil, revealed statistically significant benefits [312]. Evidence suggests that enteric-coated peppermint oil may be effective in relieving some of the symptoms of IBS [82; 307; 314].

Dyspepsia/Functional Abdominal Pain

The use of peppermint in combination with other herbals for treatment of functional dyspepsia in adults and children has been reviewed in the literature [315; 316; 317]. A study published in 2000 evaluated the safety and effectiveness of enteric-coated capsules containing a fixed combination of 90 mg peppermint oil and 50 mg caraway oil [315]. The study included 96 patients who received either one capsule twice daily or placebo for 28 days. Outcomes measured included change in pain intensity, change in sensation of pressure, heaviness and fullness, and global improvement as rated by the investigators. On the 29th day, the average intensity of pain was reduced by 40% with peppermint use, compared with 22% with placebo; pressure, heaviness, and fullness was reduced by 43%, compared with 22% with placebo; and 67% of patients were very much improved, compared with 21% with placebo.

One randomized trial investigated the pharmacokinetics of menthol use in children 7 to 12 years of age with functional abdominal pain [318]. Thirty children underwent wireless motility capsule testing, and approximately one week later, they were randomized to 180, 360, or 540 mg of enteric coated peppermint oil. The researchers observed a direct linear relationship between peppermint oil dose and menthol systemic exposure with mean elimination half-life 2.1, 3.5, and 4.6 hours for the 180-, 360-, and 540-mg doses, respectively, suggesting that a higher dose of peppermint oil may be needed to achieve maximal response [318].

A choleretic action of peppermint oil has been described, with possible applicability in the management of gallstones [82; 307]. Its antispasmodic action makes it useful in patients with colonic and esophageal spasm and in endoscopy [319; 320; 321; 322; 323].

Adverse Effects and Drug Interactions

Menthol, the major component of peppermint oil, may cause contact dermatitis in some individuals. Mucosal burns and swelling of the tongue and oral cavity have been reported following ingestion of peppermint oil. Other reported incidences include stomatitis and vulval allergic contact; however, such reactions appear to be rare [82; 304; 324; 325; 326].

Toxicology

Peppermint is generally recognized as safe. Comprehensive reports on its safety have identified the constituents pulegone and menthofuran as being of toxicologic concern [327; 328]. Use in pregnancy should be avoided due to emmenagogue effects [82].

Dosage

Doses of peppermint oil of up to 1,200 mg in enteric-coated tablets are used to treat IBS [82]. The tablets should be swallowed whole, not crushed, broken, or chewed, to avoid irritation to the mouth, esophagus, and stomach, and they should be taken 30 to 60 minutes prior to meals on an empty stomach [82; 321; 329]. Doses of 0.1–0.24 mL of peppermint oil have been used as a carminative (relieving flatulence) in clinical studies [82; 313; 330; 331].

GINGER

Efficacy: ★★★E

Safety: S

Common Name and Scientific Name

Ginger (*Zingiber capitatum, Zingiber officinale*) is also known as black ginger, ginger root, and zingiberis rhizoma. Ginger is native to tropical Asia and is a perennial that is cultivated in Australia, Brazil, China, India, Jamaica, West Africa, and parts of the United States. The rhizome is used both medicinally and as a culinary spice [82].

Historical and Current Use

The medicinal use of ginger dates back to ancient China and India. It is referred to in Chinese pharmacopeias, Ayurvedic medicine scriptures, and Sanskrit writings. Its culinary properties were discovered in the 13th century, leading to its widespread use in Europe. Apothecaries in the Middle Ages recommended ginger for travel sickness, nausea, hangovers, and flatulence. Other uses include for the common cold, fever, sore throat, gastrointestinal complications, and indigestion.

Ginger is referenced in the official pharmacopeias of more than one dozen countries. It is approved by Germany's Commission E for indigestion and to help prevent motion sickness. In the United States, ginger is approved as a dietary supplement and commonly used as a treatment for nausea [82; 332; 333; 334].

Pharmacology

Only unbleached ginger is a medicinal-grade drug, containing 1.5% or more volatile oil. More than 400 different compounds have been identified in ginger. The major constituents are carbohydrates (50% to 70%), which are present as starch. Amino acids, raw fiber, protein, phytosterols, vitamins and minerals are among the other constituents. Gingerols, a class of structurally related compounds, form shogaols, the pungent constituents of ginger. The primary shogaols are (6)-gingerol and (6)-shogaol [82; 335; 336]. Ginger exerts in vitro antioxidative, antitumorigenic, and immunomodulatory effects and is an effective antimicrobial and antiviral agent [336].

Evidence-Based Therapeutic Use and Effectiveness

Clinical trials in humans have examined the antiemetic effects of ginger as they relate to nausea of various etiologies (e.g., motion sickness, postoperative, pregnancy-related, chemotherapy-related). In particular, ginger has been found to be more effective than placebo in controlling pregnancy-related nausea and vomiting in randomized controlled trials. The mechanism by which this occurs is unclear, but enhanced gastrointestinal transport, antiserotonin activity, and possible central nervous system effects have been described in animal studies [82]. Although ginger has been shown to be effective in ameliorating pregnancy-related nausea and vomiting, its safety during pregnancy has not been established. In one randomized clinical trial, 102 participants randomly received either 500-mg ginger or placebo two times per day, 30 minutes prior to each dose of antiretroviral therapy for 14 days [337]. Forty-six (90.2%) of the patients in the placebo group and 29 (56.4%) of the patients in the ginger group experienced some degree of nausea, but the frequency of any degree of nausea was significantly lower in the ginger than the placebo group. Results from published studies on the use of ginger for chemotherapy-related nausea are equivocal [82].

Adverse Effects and Drug Interactions

Ginger may enhance the adverse/toxic effect of agents with anticoagulant/antiplatelet properties; bleeding may occur [82]. Adverse reactions reported in trials are uncommon [82]. Case reports of arrhythmia and IgE allergic reaction have been documented [334; 338].

Toxicology

Because there are little data on the toxicity of ginger in humans, there is no consensus on use during pregnancy and lactation [82]. One study found no adverse effects on pregnancy outcomes, and systematic reviews in 2013 and 2018 concurred with this conclusion [339; 340; 341].

Dosage

Ginger has been used in clinical trials in doses of 250 mg to 1 g, repeated three to four times daily [82].

SOY

Efficacy: **★E**

Safety: **No S data**

Common Name and Scientific Name

Soy (*Glycine max*), a plant in the pea family, is also known as soy isoflavones, soya, and soybean. Soy is a common source of dietary phytoestrogens found in American diets as either a food or a food additive [82; 303; 342].

Historical and Current Use

Traditional and folk uses of soy products include for menopausal symptoms, osteoporosis, memory problems, high blood pressure, high cholesterol, and breast and prostate cancer. Soy may be taken as a dietary supplement. Some studies suggest that daily intake of soy protein or soy isoflavones supplements may reduce LDL cholesterol and menopausal symptoms (e.g., hot flashes) in women; however, not enough evidence exists to determine whether soy supplements are effective for any other health uses [342].

Pharmacology

The isoflavones in soybean (i.e., genistein, daidzein, glycitein) have a chemical structure similar to estrogen. They bind to both estrogen receptors (ER alpha and ER beta) and exert estrogen-like effects under some experimental conditions [343]. Genistein, daidzein, and glycitein undergo metabolism to the isoflavandiols, equol, and p-ethylphenol. The metabolism is highly variable (i.e., dependent upon the effect of carbohydrate intake on intestinal fermentation). The isoflavones are secreted into bile via the enterohepatic circulation and eliminated in urine [82].

Evidence-Based Therapeutic Use and Effectiveness

Although soy protein has gained considerable attention for its potential role in improving risk factors for cardiovascular disease, the American Heart Association (AHA) and an expert panel from the American College of Cardiology (ACC) found that the evidence of benefit is uncertain, with a relatively small decrease (3%) in LDL cholesterol concentrations and no effect on other lipid risk factors with soy protein consumption, as compared with milk or other proteins [344].

To assess the effectiveness of phytoestrogens, including soy and soy extracts, for reducing hot flushes and night sweats in postmenopausal women, the authors of a Cochrane review evaluated the results of 30 randomized trials that had a duration of at least 12 weeks and in which the intervention for symptom relief was the use of a food or supplement with high levels of phytoestrogens [345]. However, a strong placebo effect was reported in most of the trials, with a reduction in symptom frequency ranging from 1% to 59%. The authors of the review found no evidence of effectiveness with phytoestrogen use for relief of menopausal symptoms. Authors of other studies confirm this conclusion [346; 347]. In 2017, as a result of inconclusive evidence, the FDA proposed a rule to prevent companies from claiming soy protein can reduce heart disease risk [348].

Several meta-analyses of clinical trials have evaluated the effectiveness of soy preparations in protecting against decreases in bone mineral density (BMD). Some report small improvements in BMD; others report no effect [349; 350]. Soy isoflavones, but not soy protein, may have a beneficial effect on bone turnover during early menopause and in postmenopausal women [351; 352].

Adverse Effects and Drug Interactions

Soybeans and soy products, including supplements, are generally well tolerated.

Toxicology

Concern has been expressed that feeding infants soy formula may adversely affect development of the reproductive system due to the estrogen-like activity of isoflavones; however, data are inconclusive to permit a firm conclusion [353]. In addition, some organizations, such as the American Academy of Pediatrics, assert that "isolated soy protein-based formulas are a safe and nutritionally equivalent alternative to cow milk-based formula for term infants whose nutritional needs are not met from breast milk" [354]. More research and long-term studies are necessary to determine the effects of soy-based formula.

Dosage

The effects of daily doses (40–120 mg) of isoflavones for a variety of conditions have been studied in a large number of clinical trials [82]. A dose of 20–50 g soy protein taken daily by mouth has been studied in individuals with high cholesterol. Isoflavones content has ranged from 60 mg to more than 100 mg daily [355].

CHAMOMILE

Efficacy: ★★**E**

Safety: **S**

Common Name and Scientific Name

Chamomile (*Chamaemelum nobilis*, *Matricaria recutita*) has a variety of common names, including common, English, garden, genuine, German, Hungarian, lawn, Roman, Scotch, sweet, true, and wild types [82].

Historical and Current Use

C. nobilis is a slow-growing perennial; *M. recutita* grows as an upright annual. The fragrant flowering heads of both plants are collected and dried for use as teas and extracts [82]. Both plants have been used since Roman times as antispasmodics and sedatives in the treatment of digestive and rheumatic disorders and as a wash to cleanse wounds and ulcers. Various formulations have been used to treat colic, cystitis, fever, flatulence, and vomiting [356; 357]. German chamomile flower is approved by the German Commission E for use as an inhalant in skin and mucous membrane inflammations, bacterial skin diseases (including those of the oral cavity and gums), and respiratory tract inflammations and irritations. It is also the variety most commonly used in the United States. The flower is approved for use in baths, as irrigation for anogenital inflammation, and for internal use to treat gastrointestinal spasms and inflammatory diseases [358]. *M. recutita* is widely used in Europe as a botanical for wound care. Aqueous extracts are used as washings or wet packs for fresh wounds. Alcoholic extraction yields the most complete blend, which can be transferred to aqueous formulations or ointments [359]. In Europe, traditional phytomedicines such as chamomile play an adjuvant role in acne therapy, either in addition to or in combination with intensive cosmetic care. After cleaning, creams or aqueous decoctions are applied topically [335].

Pharmacology

The chemical compounds of *C. nobilis* and *M. recutita* are similar. Chamomile tea, brewed from dried flower heads, contains 10% to 15% of the plant's essential oil. The blue-colored volatile oil is a complex mixture of sesquiterpenes, sesquiterpene lactones, and acetylene derivatives. Phenolic compounds found in the flowers include hydroxycinnamic acid derivatives, caffeic acid, and flavonoids (i.e., apigenin, luteolin, chamaemeloside). A novel and potent NK1 receptor antagonist has been identified in *Matricaria* flowers. Coumarin has also been identified [82]. The chemical constituents of chamomile (e.g., bisabolol, chamazulene) and the flavonoids apigenin and luteolin possess anti-inflammatory properties. Apigenin has also been shown to reversibly inhibit irritant-induced skin inflammation in animals and to exert antispasmodic effects in the intestines [360]. Bisabolol and the flavonoids have demonstrated antispasmodic effects [82].

Evidence-Based Therapeutic Use and Effectiveness

The chemical components in chamomile (i.e., bisabolol, flavonoids) have demonstrated antispasmodic effects in animal experiments. Chamomile infusions have been used traditionally as gastrointestinal antispasmodics despite the lack of rigorous trials to support this use [82]. Commercial preparations of creams containing chamomile are also widely available despite the paucity of trials to support their use [361; 362].

It has been suggested that chamomile might provide clinically meaningful antidepressant activity [363]. The authors of a Canadian study examined whether commercially available botanicals directly affect the primary brain enzymes responsible for GABA metabolism [364]. Approximately 70% of all extracts tested showed little or no inhibitory effect. However, both *M. recutita* and *Humulus lupulus* (hops) showed significant inhibition of GAD enzyme activity in animals.

Adverse Effects and Drug Interactions

Chamomile may be cross-allergic with what other plants?

Allergic reactions to chamomile are commonly reported and may be dependent on the route of ingestion. Hypersensitivity reactions include anaphylaxis, dermatitis, gastrointestinal upset, lacrimation, and sneezing. The dried flowering heads may induce vomiting in large amounts. Eye drops containing chamomile have caused allergic conjunctivitis [82]. Chamomile may potentiate the anticoagulant effects of warfarin. No coagulation disorders have been reported, but close monitoring of patients on anticoagulants is advised. In vitro, chamomile has been shown to be bactericidal to some *Staphylococcus* and *Candida* species [365]. Chamomile is considered safe by the FDA, but it should be used with caution in individuals who are allergic to ragweed, as cross-allergenicity may occur. Symptoms include abdominal cramping, tongue thickness, tight sensation in the throat, angioedema of the lips or eyes, diffuse pruritus, urticaria, and pharyngeal edema [366; 367].

Toxicology

Bisabolol toxicity in animal studies is reported to be low following oral administration with no noted teratogenic or developmental abnormalities [82].

Dosage

Because of the sedative effects of chamomile, caution should be used in conjunction with medications with sedative side effects or with alcohol. The oral dose is 400–1,600 mg/day in divided doses, standardized to 1.2% apigenin per dose. Chamomile is commonly consumed as a tea for its calming effect. It can be brewed using one heaping teaspoon of dried flowers steeped in hot water for 10 minutes and may be consumed up to three times per day [368].

CONCLUSION

Herbal medications have become an important issue in North America for a variety of social, economic, and medical reasons, and the use of HMs continues to increase. Data from the National Center for Health Statistics indicates that supplement use among U.S. adults 20 years of age and older increased from 48.4% to 56.1% during the period between 2007–2008 and 2017–2018, with use more common among women (63.8%) than men (50.8%) [8].

In 2012, out-of-pocket expenditures for CAM in the United States were $30.2 billion; this accounts for 1.1% of total national healthcare spending and 8.4% of total out-of-pocket expenditures [369]. The cost of dietary supplements alone was $12.8 billion, or about one-quarter of the $54.1 billion that U.S. adults spent out-of-pocket on prescription drugs [369]. Considering the high price of health insurance and changing attitudes towards CAM, the expenditures today are most likely greater.

In addition, more than 50% of patients receiving conventional medical care also use CAM [11]. An estimated 40% to 70% of patients fail to disclose the use of CAM to their healthcare providers, and concern regarding a possible negative reaction or perceived lack of interest by the healthcare provider have been identified as the main reasons for limited disclosure of CAM use [5; 11; 13]. It is commonly believed by the population in general, and by many healthcare providers as well, that due to their natural origin, these products are intrinsically safe and devoid of adverse effects or toxicity, or that the worst possible outcome is lack of therapeutic effectiveness. This has been proven false.

It is vital that healthcare providers have an understanding of the pharmacologic properties and evidence-based therapeutic efficacy of HMs. Healthcare providers should be aware of the need to inquire about and include current or past use of HMs in the patient's medical history and discuss relevant information with their patients. Providers also should be aware of the possible interactions with conventional medications and evaluate the potential therapeutic benefits of HMs when appropriate.

RESOURCES

MedWatch: The FDA Safety Information and Adverse Event Reporting Program
https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program
1-888-INFO-FDA

MedEffect Canada: Adverse Reaction and Medical Device Problem Reporting
https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html
1-866-234-2345

Natural Medicines
https://naturalmedicines.therapeuticresearch.com/

National Center for Complementary and Integrative Health: Dietary and Herbal Supplements
https://nccih.nih.gov/health/supplements

FACULTY BIOGRAPHY

A. José Lança, MD, PhD, received his Medical Degree at the University of Coimbra in Coimbra, Portugal, and completed his internship at the University Hospital, Coimbra. He received his PhD in Neurosciences from a joint program between the Faculties of Medicine of the University of Coimbra, Portugal, and the University of Toronto, Toronto, Canada. He was a Gulbenkian Foundation Scholar and received a Young Investigator Award by the American Brain & Behavior Research Foundation.

Dr. Lança participated in international courses and conferences on neurosciences. He has contributed to a better understanding of the mechanisms underlying the ontogenetic development of the brain opiatergic system. As a research scientist at the Addiction Research Foundation (ARF) in Toronto, he initiated research on the functional role played by dopaminergic cell transplants on alcohol consumption, leading to the publication of the first research reports on cell transplantation and modulation of an addictive behavior. Subsequently, he also investigated the role played by other neurotransmitter systems in the limbic system and mechanisms of reward, co-expression of classical neurotransmitters and neuropeptides and potential role in neuropsychiatric disorders.

He is an Assistant Professor in the Department of Pharmacology and Toxicology at the Faculty of Medicine and at the Faculty of Dentistry at the University of Toronto, where he lectures and directs several undergraduate and postgraduate pharmacology and clinical pharmacology courses. He was the Program Director for Undergraduate Studies in the Department of Pharmacology and Toxicology of the University of Toronto. He has developed clinical pharmacology courses for the Medical Radiation Sciences and Chiropody Programs of The Michener Institute for Health Sciences at the University of Toronto.

Dr. Lança's commitment to medical education started while a medical student, teaching in the Department of Histology and Embryology, where he became cross-appointed after graduation. In Toronto, he has contributed extensively to curriculum development and teaching of pharmacology to undergraduate, graduate, and medical students.

He has authored research and continuing education in peer-reviewed publications and is the author of six chapters in pharmacology textbooks. Dr. Lança has conducted research in various areas including neuropharmacology, pharmacology of alcoholism and drug addiction, and herbal medications.

He has developed and taught courses and seminars in continuing medical education and continuing dental education. His commitment to continuing education emphasizes an interdisciplinary approach to clinical pharmacology.

Customer Information/Evaluation insert located between pages 48–49.

Prediabetes: An Opportunity to Prevent Diabetes

Includes 7 Pharmacotherapeutic/Pharmacology Hours

Audience

This course is designed for nurses and advanced practice nurses in adult primary care, clinical, and acute care settings, healthcare and behavioral health professionals in public health and preventive medicine settings, and health education specialists.

Course Objective

Studies have shown that diabetes can be delayed or prevented in people with prediabetes, but risk reduction relies heavily on lifestyle changes on the part of the patients, making education and counseling of vital importance. The purpose of this course is to provide healthcare professionals with the information and skills necessary to effectively deal with this common condition and learn ways to help patients make healthy lifestyle choices.

Learning Objectives

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

1. Identify the incidence and prevalence of prediabetes in the United States.
2. Define the diagnostic criteria for prediabetes and diabetes.
3. Discuss major health risks associated with prediabetes.
4. Identify risk factors for diabetes and prediabetes.
5. Review the pathophysiology of type 2 diabetes.
6. Describe the results of the Diabetes Prevention Program and the associated recommendations.
7. Identify appropriate nutritional interventions to prevent diabetes.
8. Describe types of exercise and recommendations related to each for patients with prediabetes.
9. Discuss strategies and resources for helping patients select an exercise program.
10. Discuss medications used in prediabetes.
11. Evaluate the role of bariatric surgery in preventing diabetes.
12. Describe strategies to prevent diabetes in children.
13. Identify food preferences of different cultures.
14. Assist a patient in making an action plan for behavior change.
15. Outline key points included in health education for diabetes prevention.

Faculty

Susan Semb, MSN, CDCES, is a retired RN who received her Master's degree in nursing from the University of San Diego. Her nursing experience includes direct patient care, case management, staff development, program development, and health education. She spent the majority of her nursing career working as a diabetes educator in the health education department of a major health maintenance organization. Ms. Semb has also authored other continuing education courses for nurses published by NetCE and contributed to nursing books and other publications. In her retirement, Ms. Semb enjoys travel, line dancing, and pursuing an interest in antiques and vintage items.

Faculty Disclosure

Contributing faculty, Susan Semb, MSN, CDCES, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Mary Franks, MSN, APRN, FNP-C

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Sarah Campbell

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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

Prediabetes has become a major health concern in the United States. Moderately elevated blood glucose is now recognized as a significant health risk, usually preceding the onset of type 2 diabetes and increasing the risk for cardiovascular events. With this understanding, the prevention of diabetes has emerged as a standard of health care. Several research studies have shown that intensive lifestyle intervention, such as weight loss and exercise, can prevent prediabetes from progressing to type 2 diabetes and can decrease cardiovascular risk. As a result, "lifestyle medicine" and behavioral modification are becoming increasingly important facets of modern health care.

In 2019, 96 million people in the United States 18 years of age and older had prediabetes [1]. Prediabetes is defined as a blood glucose level that is higher than normal but not high enough to meet the diagnostic criteria for diabetes. Having prediabetes greatly increases the risk for later development of type 2 diabetes, and most people with type 2 diabetes have had prediabetes prior to the onset of the disease.

A landmark study published in 2002 concluded that the onset of type 2 diabetes could be delayed or prevented in some people with prediabetes [2]. It was found that weight loss and exercise were important factors that helped prevent or delay diabetes in people with higher-than-normal blood glucose who were also overweight. These findings have provided a valuable opportunity for individuals and healthcare providers to reduce the incidence of type 2 diabetes and its related morbidities.

Diabetes is a serious and costly health problem in the United States, pervading virtually all areas of healthcare practice. Efforts to prevent it can have a profound impact on healthcare spending and improve the quality of life for countless individuals. Long-term complications of high blood glucose, such as cardiovascular disease, renal failure, and retinopathy, account for the major expenditures related to diabetes care. Because these complications can take years, and sometimes decades, to fully progress, even the delay of diabetes onset would be significant.

Risk factors for the development of diabetes and prediabetes have been identified. Some of these, such as genetic predisposition and aging, are fixed and cannot be modified. Others, such as diet, body weight, and physical activity level, are changeable. Helping patients understand the changes they can make is the first step in diabetes prevention. Unfortunately, success in making and maintaining healthy lifestyle changes can be challenging. Simply giving advice is often not enough to realize actual change. Many patients are not ready to make the recommended changes, and those who initially succeed may find the changes hard to maintain. Helping a patient initiate and maintain behavior change requires an understanding of the change process and techniques for facilitating movement along the continuum of behavior change. This begins with a collaborative and patient-empowering relationship. It often requires some "letting go" on the part of the healthcare provider, who must recognize that the patient has the ultimate rights and responsibilities for his or her self-care decisions.

This course will begin by describing the significance of prediabetes and assessing the clinical information needed to provide sound health care to this population. Following this, the course will offer an abundance of evidence-based recommendations for preventing diabetes through lifestyle modification in the areas of weight management, healthy eating, and exercise. Ultimately, the goal of the program is to help healthcare professionals develop a skill set to use in promoting and supporting health behavior change in patients with prediabetes. These skills include addressing an individual's readiness to change and strategies for building motivation to change behavior. This will lead to the key points of helping patients formulate an individualized plan of action, based upon realistic goals. When these strategies are applied to interactions with patients, along with such concepts as empowerment, self-efficacy, and the stages of behavioral change, the likelihood of a successful outcome is improved. At the very least, when behavior change is not imminent, patients' ownership of their own health may be acknowledged and a partnership forged to create a path for future change.

SIGNIFICANCE OF THE PROBLEM

What percentage of the adult population in the United States has prediabetes, according to estimates from the Centers for Disease Control and Prevention?

Prediabetes is a remarkably common health problem that has been vastly underdiagnosed. The Centers for Disease Control and Prevention (CDC) estimate that 38% of the adult population in the United States has prediabetes, with 48.8% of adults 65 years of age and older having blood glucose values that meet the criteria [3]. About one in five adolescents and one in four young adults (19 to 34 years of age) in the United States has prediabetes [4]. In spite of the high prevalence of prediabetes, only 19% of people with this condition are told of their diagnosis [3].

Although it is underdiagnosed, prediabetes is a serious condition that significantly increases the risk for major health problems. People with prediabetes are approximately 5 to 15 times more likely to develop diabetes than those who have normal blood glucose levels [5]. Furthermore, the harmful effects of high blood glucose begin to occur at much lower levels than currently define diabetes. In other words, complications of diabetes begin early in the course of glucose intolerance, often before diabetes is diagnosed. Studies suggest that when blood glucose is higher than normal and remains untreated, patients

have a greater risk for developing the microvascular and macrovascular complications associated with diabetes [6; 7; 8]. For example, characteristics of diabetic retinopathy may be detected in people with no history of diabetes who have elevated fasting blood glucose or impaired glucose tolerance (IGT) [9]. Impaired glucose tolerance is also common in nondiabetic patients with peripheral neuropathy [10]. This data emphasize the importance of prompt detection and intervention of prediabetes. In fact, research suggests that restoring blood glucose levels to normal, rather than maintaining prediabetic levels, is necessary to prevent complications [7; 8]. When preventive efforts delay the onset of diabetes, there is less disease exposure and lower risk for the adverse consequences of high blood glucose over time. This results in better quality of life for the individual and lower healthcare costs for society.

Prediabetes and diabetes take a tremendous toll on the individual, society, and the healthcare system. The annual economic burden to the United States of both conditions combined exceeds $370.6 billion. In 2022, the annual burden per person averaged $12,022 for diagnosed diabetes and $955 for prediabetes [3]. This includes $413 billion in excess medical costs (e.g., physician's office and hospital visits, prescription drug costs, costly health conditions) and $106 billion in reduced productivity [3]. Spending on diabetes is expected to triple in the next 25 years [11].

In addition to monetary costs, chronic complications of diabetes significantly diminish quality of life for the individual and account for more new cases of blindness, end-stage renal disease, and lower limb amputation than any other medical diagnosis [12]. The incidence of diabetes has been steadily growing. Estimates for 2021 indicate that 38.4 million people in the United States have diabetes [3]. If obesity rates remain stable, the number of Americans with diabetes will double in the next 25 years [11]. Nearly 23% of people with diabetes do not know they have the disease [3]. According to a panel of clinical endocrinology experts, "As the prevalence of and progression to diabetes continue to increase, diabetes-related morbidity and mortality have emerged as major public health issues" [6].

Reducing the incidence of diabetes or delaying its onset provides an enormous opportunity to arrest the growth and development of this major health problem. The Diabetes Prevention Program (DPP) showed that when overweight people with prediabetes made healthy lifestyle changes, they could significantly reduce their risk for developing type 2 diabetes [2]. Healthcare professionals play an essential role in helping patients understand that they have an opportunity to prevent chronic disease and lead healthier lives.

EVALUATION AND CLASSIFICATION OF HIGH BLOOD GLUCOSE

As noted, the term "prediabetes" is used to describe blood glucose levels that are higher than normal but not high enough to be considered overt diabetes. While the term is relatively new, it is not a new disorder. Historically, healthcare providers have used various terms to describe this condition. IGT and impaired fasting glucose (IFG) are commonly used, depending upon the test used for diagnosis. In some cases, the phrase "borderline diabetes" is used, although the major authoritative bodies on diabetes and endocrinology do not provide a definition for this term. The American Diabetes Association (ADA) classifies these conditions as "categories of prediabetes" [13].

After the results of the DPP were reported in 2002, the ADA introduced the term "prediabetes" to describe nondiabetic glucose intolerance. It was felt that this name would give a better description of the meaning of the disorder and would convey that it is not a benign condition [14]. Experts anticipate that use of the term "prediabetes" will help clear up confusion among the public. A survey completed in 2006 indicated that a substantial number of people with prediabetes were unaware of it. This may be due in part to confusion brought on by the different terms used by healthcare providers [15].

BLOOD GLUCOSE TESTS

What is a normal fasting blood glucose level?

There are many tests available to assess patients suspected of having diabetes or prediabetes. These include [13]:

- Fasting plasma glucose (FPG): Blood is collected after the patient has had no dietary intake for eight hours or more. Normal fasting plasma glucose is less than 100 mg/dL.
- Casual plasma glucose: This is sometimes referred to as "random" or nonfasting blood glucose, as blood is collected without regard to the time of last caloric intake.
- Oral glucose tolerance test (OGTT): Blood is taken two hours after the person has ingested a glucose load of 75 grams. This is also known as a "glucose challenge." Normal nonfasting plasma glucose taken two hours following glucose challenge is less than 140 mg/dL.
- Hemoglobin A_{1c} (A_{1c}): This laboratory test uses venous blood to show the average blood glucose concentration over the previous two to three months. The test measures the amount of glucose that is chemically attached to the red blood cells (RBCs). RBCs that have been exposed to high amounts of glucose over their lifespan, which is about 90 days, will have more glucose attached to them. This will result in a higher A_{1c} reading. A_{1c} levels greater than 7.0% are associated with an increased risk for eye, kidney, and nerve damage and

cardiovascular disease. Historically, A_{1c} was not used as a test for the diagnosis of diabetes or prediabetes. However, in 2010 the ADA revised its criteria for the diagnosis of diabetes to include use of A_{1c} for diagnosis. A_{1c} of less than 5.7% is considered normal.

DIAGNOSTIC CRITERIA FOR DIABETES

A diagnosis of diabetes is established when a person has any or all of the following blood glucose values [13]:

- FPG: 126 mg/dL or greater
- Casual or random plasma glucose: 200 mg/dL or greater accompanied by symptoms of hyperglycemia, (i.e., polyuria, polydipsia, and/or unexplained weight loss)
- OGTT: 200 mg/dL or greater
- A_{1c}: Greater than or equal to 6.5%

DEFINITIVE CRITERIA FOR PREDIABETES

Prediabetes is an intermediate state between normal blood glucose and diabetes. The ADA specifies the following categories of increased risk for diabetes [13]:

- IFG: Fasting plasma glucose between 100 mg/dL and 125 mg/dL
- IGT: Two-hour post glucose challenge 140 mg/dL to 199 mg/dL
- A_{1c}: 5.7% to 6.4%

With regard to these categories, the ADA states, "For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range" [13].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Diabetes Association defines persons at increased risk for diabetes (prediabetes) as those with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and/or A1c 5.7% to 6.4%. Prediabetes should not be viewed as a clinical entity in its own right but rather as an increased risk for diabetes and cardiovascular disease.

(https://diabetesjournals.org/care/issue/47/Supplement_1. Last accessed January 10, 2024.)

Level of Evidence: Expert Opinion

SCREENING FOR DIABETES AND PREDIABETES

The ADA recommends testing for diabetes in asymptomatic adults who are overweight or obese and who have one or more of the following risk factors for diabetes [13]:

- First-degree relative with diabetes
- High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- History of cardiovascular disease
- Hypertension (≥140/90 mm Hg or on therapy for hypertension)
- HDL cholesterol level <35 mg/dL and/or triglyceride level >250 mg/dL
- Women with polycystic ovary syndrome
- Physical inactivity
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

Patients with prediabetes (A_{1c} ≥5.7%, IGT, or IFG) should be tested yearly. Women who were diagnosed with gestational diabetes mellitus should have lifelong testing at least every three years. For all other patients, testing for diabetes should begin at 35 years of age. If results are normal, the ADA recommends repeat testing at least every three years, with consideration for additional testing based on risk [13].

HEALTH RISKS ASSOCIATED WITH PREDIABETES

Prediabetes is not a benign condition. Both metabolic and vascular abnormalities can begin at levels less than the upper limit of what is considered normal fasting blood glucose. Most cases of type 2 diabetes are preceded by a period of blood sugar in the intermediate range of blood glucose. Many people with IFG or IGT already have microvascular complications normally associated with diabetes. Prediabetes is also associated with obesity, abnormal cholesterol, hypertension, and an increased risk for cardiovascular disease.

PROGRESSION TO TYPE 2 DIABETES

Statistics show that having prediabetes increases the risk for developing type 2 diabetes. For people with normal blood glucose, the progression to type 2 diabetes is about 5% [6]. The progression to diabetes for people with IGT is 6% to 10% per year. For persons with both IFG and IGT, the incidence of progression to type 2 diabetes is as high as 65% in six years. According to the American College of Endocrinology and the American Association of Clinical Endocrinologists (ACE/AACE), IGT should be considered a more important risk factor for progression to diabetes than IFG [6].

METABOLIC SYNDROME AND HEART DISEASE

Approximately one-half of people with IGT meet the criteria designated for metabolic syndrome. Once known as "syndrome X," metabolic syndrome is a cluster of risk factors associated with overweight and obesity that produces insulin resistance. In patients with insulin resistance, the body produces insulin, but receptor sites on liver, muscle, and adipose tissue are ineffective. When insulin resistance is present, more insulin is needed to produce a degree of glucose-lowering effect. This results in hyperinsulinemia, meaning that there are high levels of unused insulin in the blood. Hyperinsulinemia has several adverse effects on vasculature and metabolic function.

People with metabolic syndrome have twice the risk for cardiovascular disease and five times the risk for diabetes [6]. Experts anticipate that metabolic syndrome may surpass smoking as the leading risk factor for heart disease in the near future. Because of these increased risks, it is recommended that blood lipid and blood pressure goals for persons with prediabetes should be the same as those for people with established diabetes [6].

Approximately 34% of adults in the United States have metabolic syndrome, and the incidence is increasing, which is correlated with the rise in obesity rates among adults [16]. A follow-up analysis using National Health and Nutrition Examination Survey (NHANES) data from 2011–2016 found that while the overall prevalence remained essentially the same, there was a significant increase observed among young adults 20 to 39 years of age and among the Hispanic and Asian populations [17]. In addition to excess weight and sedentary lifestyle, specific genes and increased age are also associated with metabolic syndrome and insulin resistance [18].

A person may be diagnosed with metabolic syndrome if he or she has any three of the following risk factors [16; 19; 20]:

- Waist circumference more than 40 inches for men or more than 35 inches for women, indicating excess visceral fat (i.e., "apple" body shape)
- Triglycerides greater than 150 mg/dL
- High-density lipoprotein (HDL) cholesterol less than 40 mg/dL in men or less than 50 mg/dL in women
- Blood pressure greater than 135/85 mm Hg
- FPG greater than 100 mg/dL

The presence of metabolic syndrome is a signal of the need for lifestyle modification. Weight loss, exercise, and a low-fat diet can often improve metabolic abnormalities without medication. Even a reduction in sitting time and sedentary pastimes can have a positive effect on metabolic risk factors [21].

While the cluster of risk factors comprising metabolic syndrome has been recognized for a long time, there is mounting evidence that the individual risk factors alone are significant. "Metabolically healthy" obese men older than 50 years of age are still ten times more likely to develop type 2 diabetes than metabolically healthy men of normal weight. Some experts have concluded that the focus should be on treating the individual risk factors of metabolic syndrome rather than the cluster of abnormalities [22].

MICROVASCULAR COMPLICATIONS IN PREDIABETES

The risk for retinopathy and nephropathy may begin to increase when two-hour postprandial blood glucose levels reach what level?

Evidence suggests that the microvascular damage from high blood glucose begins early in the progression from normal glucose tolerance to frank diabetes. Studies of people with prediabetes indicate that risk for retinopathy, nephropathy, and neuropathy are all increased [6]. Retinal microaneurysms and microalbuminuria, the hallmarks of diabetic retinopathy and nephropathy respectively, have been detected in a significant number of nondiabetic people with IGT [9]. IGT is common in patients with peripheral neuropathy, and a causal relationship has been assumed, though not adequately studied. The risk for retinopathy and nephropathy may begin to increase when two-hour postprandial blood glucose levels reach 162 mg/dL [10].

RISK FACTORS FOR DIABETES AND PREDIABETES

What are risk factors for prediabetes and diabetes?

A number of risk factors have been identified for diabetes and prediabetes and are the same for either condition. Some risk factors are fixed or unchangeable, such as age or family history. Other risk factors are related to lifestyle choices and are therefore modifiable. The ADA has an online test that may be helpful for patients to become more aware of their personal risk for type 2 diabetes. The test may be accessed at https://www.diabetes.org/risk-test [23].

Risk factors for diabetes and prediabetes include [6]:

- Family history of diabetes (in a parent, brother, or sister)
- Previously identified as having IGT, IFG, and/or metabolic syndrome
- Belonging to certain racial and ethnic groups, including non-Hispanic Black Americans, Hispanic/Latino Americans, Asian Americans, Pacific Islanders, American Indians, and Alaska Natives
- History of gestational diabetes
- Women who have delivered a baby weighing 9 pounds or more
- Polycystic ovary syndrome (PCOS)
- Overweight

- Sedentary lifestyle
- High blood pressure (140/90 mm Hg or more) or being treated for high blood pressure
- HDL cholesterol less than 35 mg/dL
- Triglyceride level greater than 250 mg/dL
- A history of cardiovascular disease
- Receiving antipsychotic therapy for schizophrenia or bipolar disorder

HISTORY OF GESTATIONAL DIABETES

Gestational diabetes refers to diabetes that develops during pregnancy and ceases following the postpartum period. It complicates approximately 2% to 10% of all pregnancies [24]. Gestational diabetes occurs more frequently among Asian Americans, Hispanic/Latino Americans, and non-Hispanic Black Americans [25]. Other risk factors include obesity, a personal history of gestational diabetes, or a family history of diabetes. Testing for gestational diabetes should take place at the first prenatal visit if these risk factors are present. Otherwise, testing should be done between 24 and 28 weeks' gestation, usually with a glucose tolerance test [13].

Although most women with gestational diabetes will have normal glucose levels within six weeks postpartum, approximately 50% will develop type 2 diabetes in the next 10 to 20 years [24]. Therefore, regular blood glucose testing is recommended for these women during and following pregnancy. Maintenance of a healthy body weight and regular physical activity may help prevent the onset of type 2 diabetes in this population [26]. Breastfeeding in women who have had gestational diabetes is highly encouraged because it increases insulin sensitivity in the mother and can protect both mother and infant against diabetes [27].

POLYCYSTIC OVARY SYNDROME

PCOS is an endocrine disorder that affects the ovarian function of approximately 5% to 10% of women of childbearing age [28]. It is characterized by infrequent or absence of ovulation, hyperandrogenism, and/or polycystic ovaries. Signs and symptoms of PCOS include menstrual irregularities, such as amenorrhea, oligomenorrhea, or abnormal uterine bleeding. Excess androgen hormone may cause hirsutism, alopecia, and acne.

Many studies have documented an association of PCOS with insulin resistance and IGT, resulting in an increased risk for type 2 diabetes [29]. Conversion of IGT to type 2 diabetes may be 5 to 10 times more likely in patients with PCOS than in those with IGT who do not have PCOS [29]. Women with PCOS also have increased risk for cardiovascular disease.

OGTT screening for IGT is indicated upon diagnosis of PCOS and at least every two years thereafter. Because PCOS represents an independent risk factor for glucose intolerance, screening is recommended regardless of body mass index (BMI) or other additional risk factors for diabetes.

Lifestyle modification, consisting of diet, weight loss, and regular exercise, is the cornerstone of diabetes prevention in any high-risk population. There are no specific studies on prevention of diabetes in patients with PCOS. When lifestyle interventions do not achieve weight reduction, insulin-sensitizing drugs, such as metformin or a thiazolidinedione, may be considered [29].

ACANTHOSIS NIGRICANS

Acanthosis nigricans is a skin condition associated with insulin resistance. Brownish-black patches, usually found on the back of the neck, in the axillae, and other areas exposed to repeated friction, characterize this condition. The slightly raised lesions of acanthosis nigricans feel velvety to the touch. Acanthosis nigricans is especially prevalent in children with type 2 diabetes and in obese dark-skinned individuals. Parents of children with this condition often mistake it for poor hygiene and attempt to treat it with vigorous scrubbing or topical applications. As a clinical indicator of insulin resistance, the presence of acanthosis nigricans should prompt screening for type 2 diabetes [13].

FAST FOOD CONSUMPTION

A study of 44,000 Black women between 30 and 69 years of age has suggested that eating out frequently is associated with an increased incidence of diabetes onset in this population [30]. The researchers found that eating restaurant meals of hamburgers, fried chicken, fried fish, and Chinese food was independently associated with an increased risk for the development of type 2 diabetes. Study participants who reported eating hamburgers twice per week had a 40% increase in risk compared to those who did not eat any restaurant meals. Eating two meals per week of fried chicken increased the risk to 68% compared to those who had none. It should be noted that greater BMI was also associated with increased risk, suggesting that the weight gain from eating these types of foods was responsible for the increased risk for developing type 2 diabetes [30].

One study examined whether maternal intake of fried foods before conception and early pregnancy was associated with gestational diabetes [31]. The researchers found that regular intake of fried fish and fried chicken was associated with an elevated risk of gestational diabetes, whereas intake of fried potatoes, chips, or donuts was not. Another study also examined the association between pre-pregnancy consumption of fried foods and risk of gestational diabetes. This prospective study included 15,027 women in the Nurses' Health Study II cohort who were followed for 10 years. During this period, the authors documented 847 incident gestational diabetes

pregnancies. They found that frequent fried food consumption, particularly away from home, was significantly associated with a greater risk of gestational diabetes [32].

AN OVERVIEW OF TYPE 2 DIABETES

Diabetes is a disease that affects the body's ability to control and utilize its supply of glucose. Glucose, the primary fuel source for the body, originates from carbohydrate food consumption and can also be generated and regulated by the liver. When glucose is not properly regulated, blood glucose levels rise. If high blood glucose levels are sustained over time, abnormalities in the structure of blood vessels and nerves can result. This leads to organ and tissue damage and can result in serious complications affecting the eyes, kidneys, and nerves. Other pathologic processes and risk factors are strongly related to the development of cardiovascular disease, which is the leading cause of death in people with diabetes.

NORMAL GLUCOSE METABOLISM

As noted, glucose is available to the body in two ways: from food that has been consumed and through the body's own production of glucose by the liver, a process known as gluconeogenesis. Exogenous dietary glucose is ingested via carbohydrate foods, either in the form of sugars or starches. The glucose is absorbed through the wall of the small intestine, enters the circulation, and travels to the cells throughout the body. The glucose is converted to energy after passing through the cell membrane. In order for glucose to pass through the cell membrane, insulin is required. Insulin is produced by the beta cells of the pancreas, and its role is to facilitate the entry of glucose into the cells by attaching to insulin receptors. These receptors are located primarily on the skeletal muscle and liver tissue. Normally, a rise in blood glucose after eating stimulates the production of insulin from the pancreas. Other hormones, known as incretins, also help regulate glucose homeostasis after eating.

Blood glucose that is not required for immediate energy needs may be stored in the muscle and liver tissue as glycogen. Glucagon, another pancreatic hormone, controls the release of glycogen from the liver and muscle tissue.

After eating, blood glucose rises, which stimulates the production and release of insulin from the pancreas. Incretin hormones are also released from the small intestine after the ingestion of carbohydrates, even before blood glucose levels begin to rise. Incretin hormones include glucagon-like polypeptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). These incretins affect glucose homeostasis by controlling insulin and glucagon secretion during the postprandial period. Any derangement in the normal processes of glucose metabolism can cause hyperglycemia.

TYPE 2 DIABETES DISEASE PROCESS

An estimated 90% to 95% of people with diabetes have type 2 diabetes [33]. There are at least three major abnormalities of metabolism responsible for inducing the type 2 diabetes disease process: insulin resistance, insufficient insulin secretion, and inappropriate glucose production.

Insulin resistance, or the impairment of the body to effectively utilize available insulin, is the hallmark of both metabolic syndrome and type 2 diabetes. In people with early stage type 2 diabetes, insulin resistance reduces glucose uptake by 35% to 40%. With insulin resistance, the pancreas may produce normal or greater than normal amounts of insulin, but receptor sites for it are not available. For some people, the pancreas is temporarily able to make enough additional insulin to overcome the insulin resistance and produce normal blood glucose levels. Hyperinsulinemia is usually the case in early stages of type 2 diabetes and is associated with macrovascular risk factors of the metabolic syndrome, such as dyslipidemia and hypertension. High levels of insulin in the blood increase sympathetic activity that can raise blood pressure.

Insufficient insulin secretion by the pancreas usually occurs as part of the natural history of insulin resistance. When insulin resistance is prolonged, pancreatic beta cells ultimately become fatigued due to the hyperactivity required to compensate for persistent elevated blood glucose. Eventually, the beta cells can no longer produce enough insulin to meet the body's needs, and mild hyperglycemia begins to develop. Because the role of insulin is to facilitate the passage of glucose into cells, blood glucose continues to rise. Unfortunately, mild hyperglycemia is rarely symptomatic, and many people miss the opportunity to intervene with lifestyle changes that can prevent progression to type 2 diabetes at this point.

Inappropriate glucose production by the liver is a third major metabolic abnormality in diabetes. As an organ that can make or store glycogen, the liver plays a major role in regulation of blood glucose levels. In normal physiology, the liver can store glycogen and release it as needed to keep blood glucose in a normal range. In type 2 diabetes, insulin resistance of receptor sites can prevent the liver from receiving the signals it needs to stop releasing glucose when blood levels are sufficient. When this occurs, glucose output from the liver increases, causing blood glucose to continue rising inappropriately.

The presence of adipose tissue plays a role in glucose metabolism and the development of metabolic syndrome. In the past, adipose tissue was generally regarded as an inert substance that was related in some way to diabetes and cardiovascular disease. Today, fat tissue is recognized as a metabolically active organ, secreting hormones, cytokines, and enzymes that can affect functions throughout the body. In fact, fat is considered an endocrine organ.

Excessive fat cells contribute to insulin resistance. As fat cells enlarge, they become hypoxic, interfering with insulin uptake and causing collagen and fiber around the cells to increase. The resulting insulin resistance not only contributes to the development of hyperglycemia, but hypertension as well. Hepatic fat, which can lead to non-alcoholic liver disease, is more strongly related to insulin resistance than visceral fat.

LONG-TERM COMPLICATIONS

What are potential microvascular complications of diabetes?

The chronic complications of diabetes have an immense effect on the healthcare system, society, and the individual. While the economic costs of diabetic complications are enormous, their affect upon quality of life for the individual and family can be equally devastating. The CDC reports the impact of chronic complications upon Americans with diabetes as [3]:

- Leading cause of adult-onset blindness
- Leading cause of end-stage renal disease
- Significant morbidity and disability due to foot ulcer and lower extremity amputation
- Increased risk for cardiovascular disease
- Significantly increased risk for nerve disease, periodontal disease, and a host of other health problems

The chronic complications of diabetes are usually classified as microvascular or macrovascular according to the type of blood vessel damage that underlies the problem. Microvascular complications of diabetes include retinopathy, nephropathy, and neuropathy. Prolonged hyperglycemia leads to changes in the structure of the microscopic vessels that supply the eye, the kidney, and the nerves.

Macrovascular complications of diabetes are coronary artery disease, cerebral artery disease, and peripheral vascular disease. Heart disease is the foremost cause of death in people with diabetes [3]. Moreover, people with diabetes are prone to developing both coronary and cerebral vascular disease at an earlier age than people who do not have diabetes.

Much research over the past two decades has demonstrated that good glycemic control can prevent the onset and slow the progression of the chronic complications of diabetes. Maintaining an A_{1c} of 7% to 6.5% or less is recommended for most people with diabetes for the prevention of complications [13]. Furthermore, blood pressure control, healthy lipid levels, and freedom from tobacco use offer additional significant reductions in risk.

Treatments for type 2 diabetes include moderation of carbohydrate intake, weight management, exercise, medication, and stress management. Most people with diabetes perform self-monitoring of blood glucose (SMBG) on a regular basis. Diabetes management requires substantial and ongoing self-care activity on the part of the patient or caregiver. Self-management education is a hallmark of diabetes treatment and is associated with improved outcomes. These same steps should be taken in patients with prediabetes to prevent progression of the disease and sequelae.

DIABETES PREVENTION PROGRAM

The DPP was a landmark study on the prevention of diabetes. The results, published in the *New England Journal of Medicine* in 2002, reported that diabetes could be prevented or delayed in people with IFG and IGT [2]. Using subjects with prediabetes who were overweight, the study compared the results of treatment with the diabetes medication metformin versus lifestyle changes that led to weight loss. Importantly, the DPP showed that the greatest reduction in diabetes risk was associated with lifestyle changes that resulted in a 5% to 7% loss of body weight. Ten-year follow-up of DPP subjects has shown that diet and exercise, resulting in weight loss, could keep diabetes at bay for at least a decade in those at high risk [34].

STUDY DESIGN

The DPP was a multicenter study involving 3,234 subjects with prediabetes, all whom were overweight. The subjects were assigned to one of three groups:

- Lifestyle intervention group subjects were encouraged to make significant lifestyle changes related to diet and exercise. These subjects received intensive training in making these changes and professional help with behavior modification. The recommended dietary changes included calorie reduction and decreased fat intake. The exercise recommendation for these subjects was 150 minutes per week. The goal was for subjects to lose 7% of body weight and to maintain that loss.
- Metformin group subjects were assigned to take 850 mg of metformin twice per day. This group also received information about diet and exercise but did not receive the same intensive counseling as the lifestyle intervention group.
- Control group subjects were given a placebo and information about diet and exercise. Like the metformin group, this group received information without intensive counseling.

RESULTS

According to the DPP, diabetes risk reduction with the use of metformin was found to be most effective for what group?

At the end of nearly three years, the lowest incidence for developing type 2 diabetes was in the lifestyle intervention group. This demonstrates that weight loss and increased physical activity are more significant factors in diabetes prevention than the use of medication or placebo. For each study group, the approximate incidence of developing diabetes in three years was:

- Lifestyle group: 14% developed diabetes
- Metformin group: 22% developed diabetes
- Control group: 29% developed diabetes

These results indicate that millions of people at risk for type 2 diabetes could delay or prevent the disease by losing approximately 7% of their body weight through increasing exercise and eating a diet low in fat and calories. Overall, people in the lifestyle intervention group were able to reduce their risk for type 2 diabetes by 58%. After 10 years, the lifestyle group still had a 34% reduction in risk as compared to the placebo group. Reduction in risk was true for all participating ethnic groups and without regard to gender. Lifestyle modification was shown to be particularly beneficial to participants 60 years of age and older, whose risk was reduced by 71% [34; 35].

Further analyses of DPP data have concluded that changes in diet and exercise leading to weight loss have significant benefits in addition to diabetes prevention, including [35]:

- Decreased incidence in the development of metabolic syndrome
- Decrease in presence of high blood pressure
- Improvement in triglyceride and HDL cholesterol levels
- Lower levels of C-reactive protein and fibrinogen (risk factors for heart disease)
- Reduced incidence of problems with female urinary incontinence

The results of the DPP also showed that diabetes could be prevented with the use of metformin in people with prediabetes, with risk reduction of about 31% [35]. Risk reduction with use of metformin was found to be most effective for people 25 to 44 years of age and in those who had a body mass index of 35 or higher [35]. After 10 years, the incidence of type 2 diabetes was decreased by 18% in the metformin group as compared to placebo [34].

Another study, Action for Health in Diabetes (Look AHEAD), supports the findings of the DPP, showing that intensive lifestyle intervention designed to achieve and maintain weight loss produces improvements in glycemic control, as well as other health benefits. Look AHEAD is a large, 13-year study of cardiovascular morbidity and mortality in overweight or obese people with type 2 diabetes. At the four-year point, it has been found that lifestyle modifications similar to DPP recommendations can result in weight loss, reduction in blood pressure and improved lipid profile, in addition to improvement in blood glucose levels [36]. Other studies, such as the Da Qing IGT and Diabetes Study and the Finnish Diabetes Prevention Study, also provide strong evidence for the benefit of lifestyle modification in the prevention of diabetes [37].

LIFESTYLE RECOMMENDATIONS

Based on the results of several major research studies, including the DPP, the ACE/AACE make the following statement in support of preventing type 2 diabetes [6]:

> Lifestyle modification should be the cornerstone of treatment; it should be attempted with all patients and reinforced in every visit with the healthcare professional. Lifestyle is a fundamental management approach that can effectively prevent or delay progression from prediabetes to diabetes, as well as reduce both microvascular and macrovascular disease risks. Importantly, lifestyle interventions improve the panoply of risk factors for diabetes and components of the metabolic syndrome: obesity, hypertension, dyslipidemia, and hyperglycemia.

Individuals with prediabetes should be referred to an intensive behavioral lifestyle intervention program that is modeled on the DPP and/or to individualized medical nutrition therapy provided by a registered dietitian knowledgeable about diabetes care [38]. Lifestyle recommendations for people with prediabetes include [6; 13; 38]:

- A minimum 7% weight reduction, with long-term maintenance at this level
- A program of regular, moderate-intensity physical activity for 30 to 60 minutes daily, at least five days per week, or 150 minutes per week
- A diet that includes calorie restriction, fat restriction, increased fiber intake, and possible limitations in carbohydrate consumption
- Structured education and support, with regular contact, to facilitate lifestyle modification
- If overweight/obese, refer to an intensive lifestyle intervention program that includes individualized goal-setting components

Lifestyle modification is recommended for all ages, although individual adjustment may be made based on a specific patient's needs. Studies have indicated that education on lifestyle modification to prevent diabetes can be effective in either individual or group formats [6; 39].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Diabetes Association asserts that patients with prediabetes should be referred to an intensive behavioral lifestyle intervention program modeled on the Diabetes Prevention Program to achieve and maintain 7% loss of initial body weight and increase moderate-intensity physical activity (e.g., brisk walking) to at least 150 minutes per week.

(https://diabetesjournals.org/care/issue/47/Supplement_1. Last accessed January 10, 2024.)

Level of Evidence: A (Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered)

NUTRITIONAL INTERVENTIONS TO PREVENT DIABETES

General evidence-based dietary guidelines for the prevention and treatment of diabetes are to:

- Consume a variety of foods, including fruits, vegetables, grains, low-fat and fat-free dairy products, and lean meats.
- Limit food high in saturated fat, trans fatty acids, and cholesterol. Emphasize fruits, vegetables, and low-fat dairy products.
- Limit salt intake to 2,300 mg/day.
- Limit alcohol to no more than two drinks per day for men and one drink per day for women in people who choose to drink alcohol.

Increased intake of dietary fiber and whole grains may decrease the risk for developing type 2 diabetes. One study showed that replacing white rice with brown rice and other whole grains was associated with decreased diabetes risk. Investigators concluded that, for the prevention of diabetes, most carbohydrates should come from whole grains rather than refined grains [40]. In 2010, the ADA Standards of Medical Care in Diabetes were revised to specify that people at high risk for diabetes should be encouraged to consume the amount of fiber recommended by the 2015–2020 *Dietary Guidelines for Americans* (minimum of 14 g of fiber per 1,000 calories of food intake) and to consume food containing whole grains to equal at least one-half of total grain intake [12]. The ADA continues to recommend these nutritional interventions [13; 38; 41]. Nutrition counseling that works toward improving or maintaining glycemic targets, achieving weight-management goals, and improving cardiovascular risk factors within individualized treatment goals is recommended for all adults with diabetes and prediabetes [38]. Given the broad spectrum of people affected by diabetes and prediabetes, a one-size-fits-all eating plan would fail to address the varying cultural backgrounds, personal preferences, co-occurring conditions, and socioeconomic environments of these individuals. A variety of food choices and eating patterns can help people with diabetes and prediabetes achieve healthy goals and improved quality of life [13; 38].

THE MEDITERRANEAN DIET

The Mediterranean diet is based on the dietary traditions of Crete, Greece, and Southern Italy as they were practiced in the 1950s and 1960s. This was a time when the rates of chronic disease in that area were among the lowest in the world and adult life expectancy was the highest, despite the fact that medical services were limited. Ironically, it was considered a diet of the "poor" at the time, because it included small amounts of beef and processed foods, which were then valued as dietary symbols of prosperity. This traditional diet was plant-based, consisting mainly of fruits and vegetables, beans, nuts, whole grains, and fish, with moderate consumption of olive oil and red wine. It included relatively small amounts of dairy and red meat.

Scientists have studied the Mediterranean diet intensely over the past 50 years, resulting in ample evidence that the diet is associated with health benefits. Several of these studies have concluded that a Mediterranean-type diet can help prevent diabetes, assist in weight loss, prevent overweight people from progressing to obesity, lower the risk for heart disease, and decrease the need for medication in diabetic patients [42; 43; 44]. A 2009 study on the effects of the Mediterranean diet on postprandial blood glucose and lipid levels of people with type 2 diabetes has led researchers to conclude that "this kind of diet...could be considered a first line of choice for the treatment of patients with type 2 diabetes" [43]. One study of the long-term effects (8.1 years follow-up) of a Mediterranean-style diet found that it resulted in a greater reduction of A_{1c} levels, higher rate of diabetes remission, and delayed need for diabetes medication in patients with newly diagnosed type 2 diabetes [45].

General tenets of the Mediterranean-type diet include [42]:

- High consumption of fruits, vegetables, whole grains, beans, nuts, and seeds
- More than half of fat calories come from monounsaturated fats (mainly from olive oil)
- Low-to-moderate consumption of dairy products, eggs, fish, and poultry
- Very low consumption of red meat and sweets

- Moderate consumption of wine
- Being physically active and enjoying meals with others

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Diabetes Association, nutrition counseling for weight loss, including a reduction of total dietary fat and calories, is recommended for patients with prediabetes. However, evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people to prevent diabetes; therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals.

(https://diabetesjournals.org/care/issue/47/Supplement_1. Last accessed January 10, 2024.)

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

THE DASH EATING PLAN

Dietary Approaches to Stop Hypertension (DASH) is an evidence-based eating plan that has been shown to lower blood pressure in people with moderate-level hypertension, without the use of antihypertensive medication. Adhering to DASH can also result in reduced doses of medication in people with more severe hypertension [46]. This eating plan is recommended by the National Heart, Lung, and Blood Institutes and the American Heart Association and is included as an example of a healthy eating plan in the U.S. Department of Agriculture Dietary Guidelines for Americans [41]. Research has found that following the DASH eating plan can also offer protection against the development of type 2 diabetes [45; 47; 48].

The DASH eating plan emphasizes fruits, vegetables, low-fat dairy foods, whole grains, and one serving of nuts, seeds, or legumes per day. This results in increased consumption of potassium, calcium, magnesium, and fiber, nutrients that are associated with blood pressure reduction. The plan also includes moderate amounts of protein, low consumption of total fat, and decreased intake of sodium. The U.S. Department of Health and Human Services (USDHHS) has published a consumer guide that includes detailed information on how to follow the DASH guidelines, including meal plans and recipes [46]. Although not a weight-loss plan per se, evidence suggests that people can lose weight while following the DASH guidelines along with increasing physical activity. Patients can be referred to the USDHHS booklet on DASH for guidelines on lowering calories while following the DASH eating plan [46].

WEIGHT-LOSS GOALS AND RECOMMENDATIONS

Weight loss is a primary goal of prediabetes management [49]. Overweight people have a higher risk for prediabetes, diabetes, heart disease, and a number of other serious health problems. For people with diabetes and prediabetes, moderate weight loss (5% to 7% of body weight) can improve insulin action and decrease fasting blood glucose [50]. Moderate weight loss can also lower the risk for cardiovascular morbidity, associated with diabetes and prediabetes, by decreasing blood pressure and improving the lipid panel.

Reducing calories and increasing physical activity are the cornerstones of healthy weight loss [51]. Successful weight management to improve overall health requires a lifelong commitment to a healthful lifestyle that emphasizes sustainable and enjoyable eating practices and daily physical activity [49; 51]. For safe weight loss, the Academy of Nutrition and Dietetics and the ADA recommend a reduction of 500 to 1,000 calories per day to achieve a target weight-loss rate of 1 to 2 pounds per week [51].

A pivotal finding from the DPP was that diabetes could be prevented with only modest weight loss in at-risk subjects. It is notable that the weight loss target for the lifestyle intervention group was 7% of initial body weight, not attainment of ideal body weight. The actual results showed that even 5% weight loss was significant for disease prevention. For nurses and other healthcare providers, these results justify education and counseling to support modest weight loss in overweight patients. Suggesting a smaller, more achievable initial weight-loss target can help patients who feel overwhelmed by the expectation that they must lose a great deal of weight to achieve health benefits. To suggest an initial short-term weight loss goal of 5% might be a more realistic first step that is more likely to encourage and motivate patients.

ASSESSMENT OF BODY WEIGHT AND BODY FAT

Body Mass Index

BMI is a commonly used screening tool to identify weight problems and associated health risks. Calculated from a person's height and weight, BMI is highly correlated to obesity or fat mass and risk for disease, and charts and calculators are available online [51; 52; 53; 54; 55; 56]. While there are other ways to assess body fat, BMI provides a method that is inexpensive and easy to determine. Weight status categories have been developed to classify health risk based on body fat determined by the BMI [52]. Using the BMI calculation, the CDC defines weight status as follows [53]:

- Underweight: BMI less than 18.5
- Normal: BMI between 18.5 and 24.9
- Overweight: BMI between 25 and 29.9
- Obese: BMI of 30 or greater

Because it is based on a calculation from an individual's weight, BMI is not a direct measure of body fat. As an indicator of health risk, BMI is not accurate in certain populations, such as highly trained athletes, who have a higher ratio of muscle to fat, or in elderly persons who have lost muscle mass [52]. In addition, Asian populations have been shown to have a higher risk for diabetes at lower BMIs [13].

Waist Circumference

Another way to assess body fat and disease risk is to measure waist circumference. This is useful because excessive abdominal fat is a risk factor for type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease [57]. Research in the Netherlands concluded that BMI and waist circumference, when accurately measured by trained staff, are equally predictive of cardiovascular disease and mortality over 10 years [58].

Excess waist circumference with associated health risk is identified as greater than 40 inches in men or greater than 35 inches in nonpregnant women [57]. The proper way to measure abdominal circumference is to place a tape measure around the bare abdomen, just above the hipbone. The tape should be parallel to the floor and snug, but not compressing the skin. Instruct the patient to exhale and relax for the measurement [57].

NUTRITIONAL INTERVENTIONS FOR WEIGHT LOSS AND MANAGEMENT

A reduced-calorie diet is the basis for healthy weight loss. As stated, the Academy of Nutrition and Dietetics recommends a reduction of 500–1,000 calories per day, with a target weight loss of 1 to 2 pounds of weight loss per week [51]. Counseling patients on safe and effective weight loss and healthy eating includes many strategies.

Effective weight management should include assessment and intervention by a multidisciplinary team, including a physician, registered dietitian, exercise physiologist, and behavior therapist [51]. While the interdisciplinary team approach is considered the "gold standard," access to these professionals is not always feasible for patients whose healthcare plans do not cover all of these services or for those who live in remote geographic areas. In these cases, a nurse or other knowledgeable healthcare provider may assume responsibility for teaching weight reduction and healthy eating by utilizing recommendations and evidence-based practice standards from these other disciplines. Research evidence supports that a relatively inexpensive program involving nurse support is as effective as a more resource-intense program for weight maintenance over a two-year period [59].

The following information is not intended, nor is it able, to replace the specialized training and knowledge of a registered dietitian or other specialists in weight management. However, because these resources are not always available, the information provided here can serve as a guide to nutrition education for the prevention of diabetes.

Reduction in Fat and Calories

Achieving a healthy weight requires a diet that has a total energy (or caloric) intake that is less than energy expended by metabolism, physical activity, and exercise. The average American diet consists largely of energy-dense, nutrient-poor foods with added sugars and solid fats, including grain-based baked goods, such as cookies, cakes, and yeast breads. Soft drinks represent another major source of calories in the typical American diet. Less than 6% of daily calories should come from these sources, and while intake has decreased across all age groups and for both genders, it still exceeds the limit recommended by the USDA [60].

There has been much debate about the risks and benefits of restricted carbohydrate diets, especially for people with diabetes and prediabetes. While the issue has not been fully resolved, evidence suggests that excessive total caloric intake, not carbohydrate intake alone, contributes most to the development of insulin resistance by causing weight gain. For this reason, prevention of weight gain, not carbohydrate restriction, is the recommended approach for preventing insulin resistance.

General guidelines for fat and calorie reduction include:

- Trim all fat from beef and pork and remove skin from chicken.
- Use non-fat or low-fat dairy products.
- Bake, broil, or grill food instead of frying.
- Use low-fat dressings and spreads.
- Limit saturated fat, avoid trans fat, and use moderate amounts of canola or olive oil.
- Limit sweets and desserts.
- Limit fast food and restaurant meals.
- Limit high-calorie snacks such as chips and granola bars.
- Eat more slowly.
- Leave some food on the plate.
- Replace caloric drinks, such as juice, energy drinks, and soda, with water.
- Use measuring spoons and cups to control portion sizes.

Portion Control

Which interventions may be effective in helping patients better control portion sizes?

The term "portion distortion" refers to the perception that the amount of food served on a plate or at any single eating occasion is the appropriate amount to eat, no matter the size. It has been shown that people who eat too much at one time do not compensate by eating less later in the day. Furthermore, larger portion sizes override hunger and satiety signals, so eating continues beyond the feeling of fullness [21; 51]. Portion distortion is reinforced in society by restaurants that serve large helpings, food sold in large packages, and larger size plates and eating utensils.

Studies indicate that portion control is a valid component of a healthy and effective weight loss plan. Based on these studies, the Academy of Nutrition and Dietetics recommends that portion control be integrated into the weight-loss plan. To help patients with portion control, advise them to [61]:

- Read Nutrition Facts labels to identify appropriate serving sizes.
- Eat from a plate, not a package. Avoid eating directly out of a bag or bowl. Put one serving on a plate or dish.
- Try portioning out foods with measuring cups and spoons to get an idea of what the serving size looks like (***Table 1***). Compare these serving sizes to the sizes of everyday objects (***Table 2***).
- Use smaller plates, bowls, and utensils for eating.
- Be aware of large serving sizes in restaurants. Place half of a large portion in a take-home container before starting the meal or share an entree with another person.
- Practice the "plate method" of portion control.

The Plate Method

A group of dietitians in Idaho developed the Idaho Plate Method in 1993, based upon an earlier model from Sweden [64]. Since its inception, the plate method has been widely utilized in health education as a practical and effective way of teaching healthy eating behavior [41; 65; 66; 67]. Its premise is that healthy eating and controlling portion sizes can be simplified by using a visual image. While incorporating the nutritional recommendations from the ADA, the plate method helps people with diabetes lose weight, reduce the incidence of hypoglycemia, and make better food choices [41; 66]. Information regarding the Idaho Plate Method may be accessed online at http://www.platemethod.com.

This method has since been modified specifically for patients with diabetes. The Diabetes Plate Method is a useful visual to assist in portioning meals without measuring (***Figure 1***). The teaching tenets of the Diabetes Plate Method are [64; 65]:

- Use a nine-inch plate.
- Fill approximately half the plate with non-starchy vegetables, such as leafy greens, onions, peppers, tomatoes, cucumbers, green beans, broccoli, carrots, cauliflower, or mushrooms.
- Fill one-fourth of the plate with protein foods, such as lean cuts of meat, fish, poultry without the skin, tofu, one to two eggs, 2 ounces of low-fat cheese, one-third cup nuts, or 2 tablespoons of peanut butter.
- Fill one-fourth of the plate with carbohydrates, such as whole-grain bread, brown rice, whole-grain pasta, potato, beans, lentils, corn, peas, fruit, dried fruit, or yogurt. This section may also be replaced with a glass of milk.
- Choose water or a low-calorie drink, such as unsweetened tea or coffee, sparkling water, or diet drinks.

The plate method is very helpful as a first step in learning to control portion sizes and to choose healthy foods in the right amounts. It is useful for patients who are busy or overwhelmed by too much information and for those who do not like strict regimens. People of low-literacy and those who have barriers to weighing and measuring foods may find the plate method the most acceptable approach to healthy eating and weight management [64; 65].

MyPlate

In 2011, the USDA Center for Nutrition Policy and Promotion released the *2010 Dietary Guidelines for Americans*, which place greater emphasis on promoting the consumption of nutrient-dense foods and to achieving and maintaining a healthy weight. These guidelines were updated in 2020 and now recommend personalizing an individual's food plan based on age, sex, height, weight, and physical activity level. Information about the MyPlate Plan is available at https://www.myplate.gov [41; 68].

The MyPlate Plan illustrates a plate being one-half filled with vegetables and fruits (***Figure 2***). By comparison, the Plate Method shows one-half of the plate filled with vegetables only and fruit included in the carbohydrate section. Both plates display one-fourth filled with lean protein [65]. The MyPlate Plan also includes one-fourth of the plate filled with grains, of which at least one-half should be whole grains. In addition, a serving of low-fat or fat-free dairy milk or yogurt (or lactose-free dairy or fortified soy version) may be added. All foods and beverages should contain limited amounts of added sugars, saturated fat, and sodium [41].

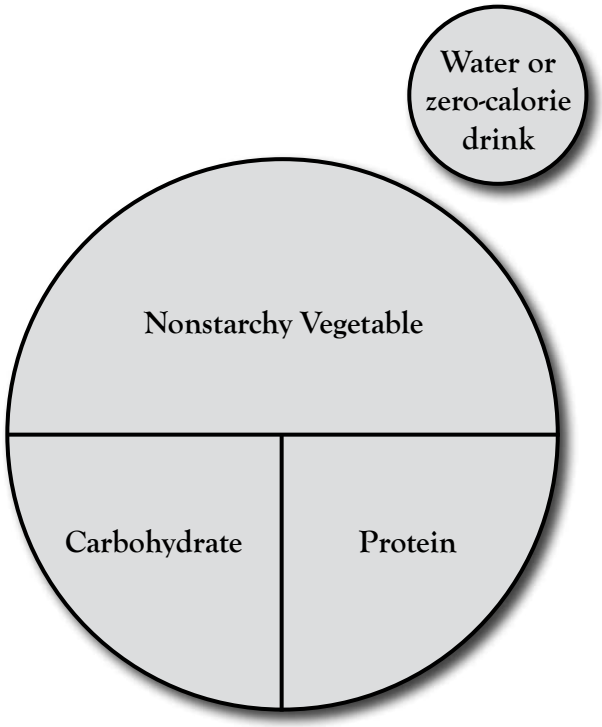
GUIDE TO SERVING SIZES FOR MEAL PLANNING	
Category	**One Serving Size**
Bread	1/4 large bagel (1 oz.) 1 biscuit (2.5 inches across) 2 slices (1.5 oz., reduced-calorie, light) 1/2 English muffin 1/2 hot dog or hamburger bun 1 4-inch pancake 1/2 of 6-inch pita 1 6-inch corn tortilla 1 4-inch waffle square
Cereals and grains (including pasta and rice)[a]	1/3 cup barley, couscous, pasta, quinoa, rice (white, brown, other types and colors) 1/2 cup bulgur, tabbouleh, wild rice 1/2 cup bran cereal or shredded wheat 1/4 cup granola 1/2 cup hot cereal (oats, oatmeal, grits) 3/4 cup unsweetened ready-to-eat cereal
Starchy/non-starchy vegetables	1/2 cup cooked corn, green peas, mixed vegetables, parsnips 1/2 cup marinara or spaghetti sauce 1/4 large (3 oz.) baked potato, with skin 1 cup (2 oz.) French-fried (oven-baked, skin on) potato 1/2 cup mashed potato (with milk and fat) 1 cup winter squash 1/2 cup yam or sweet potato 1/2 cup cooked vegetables 1 cup raw vegetables 1/2 cup vegetable juice
Fruits	1/2 cup unsweetened applesauce 1 extra-small banana 3/4 cup blueberries 2 Tbsp dried fruits 1/2 cup canned fruit 1 small fruit (e.g., whole apple) 1/2 cup unsweetened fruit juice 17 small grapes (3 oz.) 1 cup diced melon 1 1/4 cups whole strawberries
Milk and milk substitutes	1 cup milk (nonfat, 1%, 2%, whole) 2/3 cup plain or sweetened yogurt 1 cup rice drink, plain, fat-free
Meat and other proteins	1 oz fish, chicken, or beef (cooked) 1/4 cup cottage cheese 1 egg 1 Tbsp peanut butter 1/2 cup tofu

Table 1 continues on next page.

GUIDE TO SERVING SIZES FOR MEAL PLANNING *(Continued)*	
Fats and oils	1 tsp oil 1 tsp butter or margarine 2 Tbsp avocado 1 Tbsp regular salad dressing 1 tsp regular mayonnaise 1 Tbsp light mayonnaise
Sweets and desserts	1/2 cup ice cream 1 1/4-inch square brownie, unfrosted 2 small cookies 3 pieces hard candy 1/2 cup sugar-free pudding 2-inch square unfrosted cake
[a]Serving sizes for grains and pasta measure cooked foods.	
Source: [62]	*Table 1*

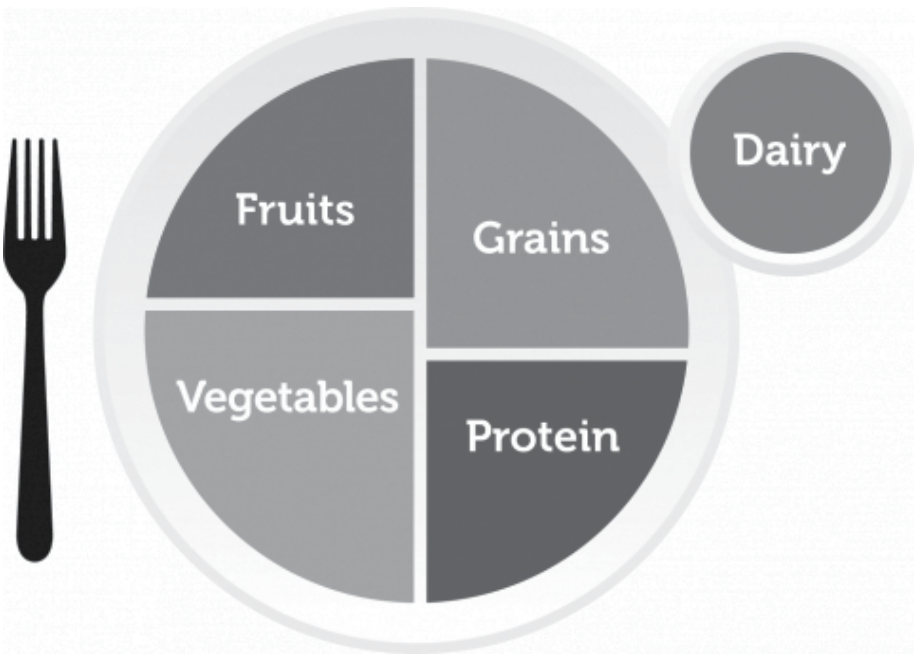
SERVING SIZES AS COMPARED TO COMMON OBJECTS	
Serving Size	**Is The Same Size As**
Grain Products	
1 pancake	CD or DVD
1/2 cup cooked, rice, or pasta	1/2 baseball
1 cup cereal flakes	Fist
1 slice bread	Cassette tape
1 piece cornbread	Bar of soap
Meat/Fish/Poultry/Protein	
3 oz. meat, fish, and poultry	Deck of cards
3 oz. grilled/baked fish	Checkbook
2 Tbsp. peanut butter	Ping pong ball
Vegetables/Fruit	
1 cup salad greens	1 baseball
1 baked potato	Fist
1 med. fruit	1 baseball
1/2 cup fresh fruit	1/2 baseball
1/4 cup raisins	1 large egg
Fats	
1 tsp. margarine or spreads	1 die or the tip of your thumb
Dairy/Cheese	
1.5 oz cheese	4 stacked dice or 2 cheese slices
1/2 cup ice cream	1/2 baseball
Source: [63]	*Table 2*

THE PLATE METHOD



Source: [64; 65] *Figure 1*

THE MYPLATE PLAN



Source: [68] *Figure 2*

Eating Frequency

The Academy of Nutrition and Dietetics recommends that for weight loss and maintenance a registered dietician nutritionist "should individualize the meal pattern to distribute calories at meals and snacks throughout the day, including breakfast" [51]. Earlier recommendations maintained that eating small meals at regular intervals (four to six meals/snacks per day) could help maintain glucose levels; however, recent studies have not shown that higher eating frequency produces greater weight loss, and, for some, three meals per day leads to a significant reduction in A_{1c}, appetite, and overall glycemia, with a decrease in daily insulin and improved glucose metabolism [51; 66; 67]. The most important counseling strategy is to help the person find a meal pattern that prevents times of heightened hunger, particularly in situations in which high-calorie food choices are readily available. For example, helping the patient plan healthy sack lunches and snacks may prevent overeating at vending machines or fast food establishments during working hours. Consuming a greater proportion of calories early in the day, as opposed to in the evening, may also prove to be beneficial to patients' weight loss goals [51].

Eating breakfast can have a positive influence on appetite control, food choices, and metabolism, and thus help with weight management [21; 51; 69]. Eating breakfast helps an individual avoid becoming overly hungry early in the day, which can later lead to overeating and poor food choices. A healthy breakfast also can set the psychologic and behavioral tone for the day, prompting better food choices overall. For patients who work shift hours, eating within one hour of waking can be considered "breakfast" regardless of the time of day it is eaten.

Meal Replacements

Meal replacements include drinks, bars, and other packaged portion- or calorie-controlled items. Use of meal replacements, along with an overall program of calorie control and regular exercise, may enhance weight loss by as much as 8.5% [70; 71]. Meal replacements can be helpful to people who have difficulty with portion control, who need the convenience of quick and easy nourishment, and/or who feel overwhelmed with the variety and easy availability of calorie-dense foods. Meal replacements can be used to substitute for one or two meals or snacks per day when appropriate for the individual's lifestyle. Meal replacements used for weight loss should be balanced with conventional foods to optimize the overall nutritional content of the individual's diet [51].

Label Reading

Knowing how to read the Nutrition Facts labels (***Figure 3***) can help patients make informed food decisions to choose a healthy diet and help with weight management and diabetes prevention [72; 73; 74]. A 2016 redesign of the Nutrition Facts label includes larger, bolder type for the number of servings; updated serving sizes; calories listed in larger type; updated Daily Values (and a footnote explaining them); a new fact indicating "added sugars;" and a change to the nutrients required section, with amounts (in percentages) declared [75].

SAMPLE NUTRITION FACTS LABEL

Nutrition Facts

8 servings per container

Serving size **2/3 cup (55g)**

Amount per serving

Calories **230**

	% Daily Value*
Total Fat 8g	**10%**
Saturated Fat 1g	**5%**
Trans Fat 0g	
Cholesterol 0mg	**0%**
Sodium 160mg	**7%**
Total Carbohydrate 37g	**13%**
Dietary Fiber 4g	**14%**
Total Sugars 12g	
Includes 10g Added Sugars	**20%**
Protein 3g	
Vitamin D 2mcg	10%
Calcium 260mg	20%
Iron 8mg	45%
Potassium 235mg	6%

* The % Daily Value (DV) tells you how much a nutrient in a serving of food contributes to a daily diet. 2,000 calories a day is used for general nutrition advice.

Source: [75] *Figure 3*

Instruct patients to consider the following when reading Nutrition Facts labels [74; 76]:

- Check the serving size (the amount typically eaten at one time) and the number of servings per package. Compare your individualized portion size to the serving size. If the label indicates a serving size of one cup and you eat two, you are consuming twice the calories, fat, and other nutrients than that listed on the label.

UNDERSTANDING NUTRITION TERMS	
Term	**Definition**
Low calorie	40 calories or less per serving
Low cholesterol	20 mg or less and 2 g or less of saturated fat per serving
Reduced	At least 25% less of specified nutrient or calories than the usual product
Good source of	Provides at least 10% to 19% of DV of a particular vitamin or nutrient per serving
Excellent source of...	Provides at least 20% or more of DV of a particular vitamin or nutrient per serving
Calorie free	Less than 5 calories per serving
Fat free/sugar free	Less than 1/2 g fat or sugar per serving
Low sodium	140 mg or less of sodium per serving
High in	Provides 20% or more of DV of a specified nutrient per serving

Source: [76] *Table 3*

- Note the number of calories in a single serving. Compare calories and fat grams per serving among different products and choose foods that are lower in fat and calorie content per serving. Understand nutrition terms (***Table 3***).
- Let percent of Daily Values be a guide to assess how a particular food fits into your daily meal plan. A Daily Value of 5% or less is low; 20% or more is high. Percent of Daily Values is for an entire day, not just one meal or snack, and are average levels of nutrients for someone consuming 2,000 calories/day, which may be more or less than you need.
- Choose foods that are low percentage Daily Values in saturated fat, "added sugars," and sodium to reduce your risk of chronic disease. The recommended daily intake of sodium is 2,300–2,400 mg or less (with 2,000 mg or less often recommended for people with certain cardiac conditions). Aim for entrees with less than 600 mg sodium per serving, side dishes with less than 400 mg, and snacks with a maximum of 200 mg of sodium per serving.
- Avoid foods that list trans fat on the label. Trans fats originate from the process of hydrogenating oil. The goal is to consume zero trans fats.
- Aim for foods with high percentage Daily Values of fiber, potassium, vitamin D, calcium, and iron, and include foods with more of these nutrients in your daily meal plan.
- Understand the additional nutrients (e.g., protein, carbohydrates, sugars). Eat these foods in moderation. A daily percentage Daily Values for protein is not required on the label. Carbohydrates include sugars, starches, and fiber. Fiber is beneficial for weight loss and blood glucose control. A product is considered a good source of fiber if it has 2.5–4.9 g fiber/serving. Foods can officially be labeled "high fiber" if they contain at least 5 g fiber/serving. Whole-grain breads, grains, and rice are the healthiest choice. Total sugars includes those naturally present in many nutritious foods and beverages (e.g., milk, fruit)."Added sugars" are added during the processing of foods. Avoid foods containing high amounts of added sugars.
- Ingredients are listed in order from most to least. Highly processed foods usually have a long list of ingredients; healthier choices often have shorter ingredient lists.

The U.S. Food and Drug Administration (FDA) provides a sample Nutrition Facts label that can be used to check a patient's label-reading skills [77].

While the FDA regulates food label claims, consumers should be aware of marketing ploys that can be misleading. Many packaged foods make health statements such as "light" and "all natural," but some of these claims and terms are not approved by the FDA. For example, claims such as "all natural," "doctor-recommended," and "strengthens your immune system" are not FDA approved.

Food Diaries

Authorities on healthy eating and weight loss recommend using a food diary to keep track of what is eaten, including the number of calories consumed each day, to stay on track with making healthy choices and to record environmental and internal cues that are associated with what one eats. A food diary also can give the patient's healthcare provider a quick way to check weight loss progress and to help patients identify unhealthy eating habits and find healthier, alternative solutions [46; 78; 79]. Some examples of healthy, reduced-calorie substitutions include:

- Use non-fat milk and/or sugar-free syrup in coffee.
- Drink sugar-free, reduced-calorie hot chocolate made with water or fat-free milk in place of a sweet dessert.
- Use slow-churned, reduced-calorie ice cream or fat-free frozen yogurt in place of regular ice cream.
- Eat raw vegetables with salsa or fat-free dressing instead of chips.

- Use mustard or a small amount of oil with vinegar on sandwiches instead of mayonnaise.
- Substitute fatty lunch meats, such as bologna, with low-fat lunch meats that are 95% to 97% fat free.
- Use Canadian bacon instead of bacon or sausage.
- Replace refried beans with cooked or canned kidney or pinto beans.
- Select pasta with red sauce (e.g., marinara) instead of white sauce (e.g., Alfredo).
- Top baked potatoes with salsa or fat-free sour cream in place of butter.

A 2008 study showed that keeping a food diary can double weight loss [78]. In this study, nearly 1,700 overweight or obese adults were enrolled in a long-term weight-loss program that included group sessions with nutrition and behavior experts. At the end of six months, those who kept a food diary lost an average of 18 pounds, compared to 9 pounds for those who did not [78].

Rating Hunger

Behavioral interventions for weight loss and healthy eating include helping patients understand why they eat. In some cases, patients eat in response to cues other than hunger (e.g., a television ad, social events, smells from a food court). They simply fail to differentiate between when their body needs food and when it does not.

Genuine hunger is represented by stomach pangs or growling, emptiness in the stomach, irritability, headache, low energy/fatigue, and difficulty concentrating [80]. The ADA suggests that, prior to eating, patients rate their hunger to determine if they are genuinely hungry or whether they are eating in response to an emotion [80]:

- Full: A rating of 6 (comfortably full) to 10 (stuffed/feeling sick)
- Neutral: A rating of 2 (very hungry/unable to concentrate) to 5 (comfortable; neither hungry nor full)
- Hungry: A rating of 1 (starving, dizzy, irritable)

Alternatives to eating when not truly hungry include [80]:

- Drinking a glass of cold water or a zero-calorie beverage
- Taking a walk to change the scenery
- Exercising
- Reading a book or magazine
- Working on a hobby
- Playing a game with someone

FOODS TO ENCOURAGE

As stated, people eat for a variety of reasons. The quantities, proportions, and variety or combination of foods, drinks, and nutrients in individual diets and the frequency with which they are consumed constitute dietary patterns. According to the 2020–2025 *Dietary Guidelines for Americans*, the dietary patterns that are associated with beneficial outcomes for all-cause mortality, overweight/obesity, and type 2 diabetes include higher intakes of fruits and vegetables, legumes, whole grains, low- or non-fat dairy, lean meat and poultry, seafood, nuts, and unsaturated vegetable oils [60]. Plant-based diets (i.e., eating patterns that avoid the consumption of most or all animal products and support a high consumption of fruits, vegetables, legumes, seeds, whole grains, and nuts) have been shown to significantly and positively impact the management of diabetes [81].

Fruits and Vegetables

For most Americans, intake levels of fruits and vegetables are lower than those recommended in the 2020-2025 *Dietary Guidelines for Americans*. These low intakes contribute to the underconsumption of nutrients and food components, including fiber, potassium, and vitamins A, C, and K [60]. Fruits and vegetables help maintain fullness while reducing caloric intake. Patients can begin increasing vegetable intake by including an additional serving at both lunch and dinner. Healthy toppings for vegetables may include lemon juice, fat-free sour cream, vinegar, and/or non-caloric butter substitutes. Fruit intake can be increased by substituting fresh fruit for sweet snacks. Fruits and vegetables can be a good source of fiber, which is also an essential part of a healthy diet.

Whole Grains

A diet rich in whole grains can reduce the risk for several chronic health conditions, such as obesity, metabolic syndrome, diabetes, and cardiovascular disease. It is also associated with lower body weight and decreased blood pressure. One study reported that diets with high amounts of whole-grain foods helped achieve significant weight loss and reduced the risk for cardiovascular disease and diabetes [82]. A grain is considered "whole" when the entire grain seed is intact. The bran and germ components, which contain most of the fiber and nutrients, are removed during the refining process. Good sources of whole grains are whole-wheat breads, whole-wheat pasta, brown rice, barley, oats, whole-grain cereal, and legumes. Instruct patients to read bread and cereal labels and look for the word "whole" in the ingredient list. If "whole grain" or "whole wheat" is the first ingredient listed, there is a good chance that this item will be an excellent source of whole grain. "Enriched" wheat usually indicates that the grain is refined. If a bread or cereal product has enriched wheat listed as the first ingredient, it is not a good source of whole grain [83].

Polyunsaturated Fatty Acids

Polyunsaturated fatty acids, such as omega-3 fatty acids, improve insulin sensitivity and may help reduce risk for cardiovascular disease by reducing triglycerides, increasing HDL cholesterol, and lowering blood pressure [21]. Good sources include salmon, sardines, herring, trout, and other fatty fish, as well as fish oil supplements. The ADA recommends an eating plan that is rich in monounsaturated and polyunsaturated fats to improve glucose metabolism [13]. Dietary guidelines recommend consuming at least two servings of non-fried fatty fish per week [68]. Linolenic acid is another type of polyunsaturated fatty acid and one of the three main omega-3 fatty acids that is believed to decrease blood clotting and inflammatory processes in the body. Because it cannot be synthesized by humans, it is considered essential in the diet [60]. Primary sources are canola oil, soybean oil, walnuts, flaxseed, and olive oil. Keep in mind that unsaturated fats contain the same amount of calories as saturated fat and that the diet should consist of no more than 10% of calories from fat [60].

SUSTAINING WEIGHT LOSS

The U.S. Preventive Services Task Force (USPSTF) analyzed four types of weight-loss interventions: behavior-based weight loss (80 trials); behavior-based weight loss maintenance (9 trials); pharmacotherapy-based weight loss (32 trials), and pharmacotherapy-based weight loss maintenance (3 trials) [84]. The Task Force found moderate evidence supporting intensive, multicomponent behavioral interventions in obese adults. Such interventions can lead to clinically significant improvements in weight status and can reduce the incidence of type 2 diabetes. The USPSTF recommends that adults with a BMI of 30 or higher be referred to intensive, multicomponent behavioral interventions for weight loss support and maintenance [84].

The research reviewed by the 2020 Dietary Guidelines Advisory Committee supports a lifespan approach to nutrition, beginning in the earliest stages of life and continuing into adulthood [60]. A lifespan approach reinforces the importance of implementing dietary patterns (from birth to adulthood) that are most associated with adequate nutrition for every life stage. Each life stage provides individuals (or their parents) with the opportunity to make food choices that promote health and well-being, achieve and maintain appropriate weight, and reduce the risk of diet-related chronic disease. A dietary patterns approach also allows for accommodations for cultural, personal, and individual needs and food choice preferences [41; 60].

EATING BEHAVIORS AND PROBLEM SOLVING

As discussed, food and eating serve many purposes and have multiple meanings for people. For example, eating can provide socialization, emotional comfort, and relief from stress and anxiety. Eating also can be driven by environmental cues and other external forces.

Behaviors associated with overweight and obesity include excessive television watching, decreased physical activity, frequent eating at fast food restaurants, consuming foods high in fat and sugar, skipping breakfast, and lack of portion control. Effective weight loss counseling includes exploring the behavioral components of a patient's dietary habits and assisting with problem solving. Mindful eating is a valuable skill that can result in healthier lifestyle habits. The food diary and the hunger scale are useful tools for increasing awareness of one's actual physical need for food and for monitoring the quantity of food consumed.

Nutritional counseling should provide help in understanding reasons for "emotional eating." This includes helping patients identify feelings related to eating and determining where the feelings originate. It may involve encouraging the patient to respond to feelings in ways other than eating. For example, if the patient identifies that he or she is bored, explore other enjoyable activities that could be done instead of eating. If a patient is depressed, provide sources of support for that problem. Thorough assessment may reveal the need for a mental health referral for help with emotionally rooted eating behaviors.

The Association of Diabetes Care and Education Specialists (ADCES) recommends asking patients the following questions to help with problems related to eating behavior [85]:

What three words fill in the blanks for you? When I think about healthy eating, I feel _____, _____, and _____. This question helps examine the emotions the patient has about eating and that he or she may have toward making behavior changes. If this exploration reveals barriers, it is best to ask the patient first what he or she believes will help to overcome it. The next step is to offer suggestions to enhance the patient's own ideas, if indicated.

What did you eat for dinner last night? Is there anything you could have done to make your meal healthier? These questions help assess patients' food preferences and increase their awareness of what they are eating. By asking patients to generate their own ideas for improvement, they are empowered to make behavior changes on their own behalf.

For you, what is the hardest part about healthy eating? This question enables patients to identify challenging situations and to solve problems. Healthcare professionals can guide them in making their own plan to avoid the identified problems or to be prepared to make better choices when an unavoidable situation arises.

What is the best part about healthy eating? When patients make their own statement about how change will be beneficial, it facilitates readiness. This is a powerful component of motivational interviewing, which is discussed more thoroughly in a later section of this course.

A step-wise approach to behavioral problem solving also can be helpful. Kaiser Permanente Health Education Services recommends the following sequence for behavioral problem solving [86]:

- Define the problem: Problem identification should be patient-centered. Ask the patient "What concerns you most?" and ask him or her to identify what would be good about making the change.
- Find solutions: Ask patients to list options for how the problem could be solved. If resistance to change is evident, maintain empathy and remain nonjudgmental. Ask what might help the patient become more ready to find solutions.
- Choose a solution: Of the possible solutions, instruct the patient to select the best one and make it a goal. Reflect back what the patient has said about the pros and cons of the various options.
- Evaluate progress after one week: If not successful with the chosen plan or solution, patients should consider modifying the original goal or looking at other options from the list. Explore how these other options might be put into action.

EXERCISE TO PREVENT DIABETES

An important finding from the DPP and other studies on diabetes prevention is that exercise is integral to lifestyle modification for the prevention of diabetes. In the DPP, subjects in the lifestyle intervention group participated in at least 150 minutes of moderate physical activity per week. Following the results of the DPP and other studies, the ADA now recommends 150 minutes of moderate-to-vigorous intensity physical activity per week, along with a healthful diet and a program of weight control, for the prevention of type 2 diabetes [13]. For improved health and wellness in general, the American College of Sports Medicine (ACSM), the American Heart Association, and the USDHHS all recommend 30 minutes of moderate-intensity physical activity five or more days per week, or a minimum of 150 minutes per week for adults [87].

PRE-EXERCISE HEALTH EVALUATION

While there are no specific recommendations for evaluating the person with prediabetes for exercise clearance, guidelines do exist for people with diabetes and other chronic conditions. The ADA recommends that people with diabetes should be assessed before beginning a program of physical activity if it is going to be more vigorous than brisk walking. This assessment should include looking for conditions that may be associated with increased likelihood of cardiovascular disease. However, the circumstances under which a graded electrocardiogram (EKG) stress test should be considered are not well defined. Cost analysis studies have indicated that the widespread use of this test is cost-prohibitive, partly due to high risk of false-positive results, which trigger subsequent invasive testing procedures. The recommendation is that medical providers weigh the potential benefits of this type of testing against risks and costs in each individual case.

Pre-exercise medical clearance is not necessary for asymptomatic individuals receiving diabetes care consistent with guidelines who wish to begin low- or moderate-intensity physical activity not exceeding the demands of brisk walking or everyday living. Individuals who plan to increase their exercise intensity or who meet certain higher-risk criteria may benefit from referral to a healthcare provider for a checkup and possible exercise stress test before starting such activities [88].

BENEFITS OF EXERCISE

Studies indicate that most people with type 2 diabetes show decreases in blood glucose after mild-to-moderate exercise [89]. The magnitude of glucose lowering is proportionate to the duration and intensity of the exercise and persists into the post-exercise period, prolonging its benefits over two to three days [89]. Another noteworthy benefit of regular exercise is the reduction of risk factors for cardiovascular disease, such as hypertension, insulin resistance, and dyslipidemia.

Exercise improves carbohydrate metabolism and insulin sensitivity. It reduces blood glucose by lessening the production of glucose by the liver and by increasing blood glucose utilization by the skeletal muscle. Improvement in insulin sensitivity from a single bout of exercise lasts 24 to 72 hours, depending on the duration and intensity of the exercise [89]. Exercises that increase muscle mass, such as resistance exercises, can lead to enhanced glucose metabolism, as greater muscle mass is associated with better insulin uptake.

Besides lowering blood glucose, improvement in insulin sensitivity also mediates the negative effects of metabolic syndrome, reducing such cardiovascular risk factors as hypertension, hyperinsulinemia, central obesity, lipid disorders, and inflammatory markers such as C-reactive protein [89]. Other health benefits related to regular physical activity include reduced risk for osteoporosis, obesity, colon cancer, breast cancer, peripheral vascular disease, anxiety, and depression. For older adults, regular exercise is also associated with a reduced risk of falls and injury [89].

EXERCISE AND WEIGHT LOSS

Successful weight loss and long-term maintenance of lost weight require a combination of healthy nutrition, regular exercise, and behavior modification. Research shows that weight loss is more likely to occur as a result of decreased calories in the diet than from calorie burning during exercise. This is because it is very difficult for most people to create the 500 to 1,000 calorie per day deficit needed for weight loss with exercise alone [51].

The benefit of exercise to weight loss is considered "dose related," meaning that greater weight loss and less weight regain are associated with increased amounts of exercise. Moderate-intensity physical activity for between 150 and 200 minutes per week is effective in preventing weight gain, but it will not result in clinically significant weight loss without calorie restriction. Amounts of moderate-intensity physical activity beyond the recommended 150 minutes per week are usually necessary to bring about significant weight loss in the absence of calorie restriction. According to the ACSM, 200 to 300 minutes of exercise per week will provide modest weight loss. Specifically, 225 to 420 minutes (approximately four to seven hours) of moderate exercise per week are associated with weight loss of roughly 11 to 16 pounds over several weeks [90].

Although evidence suggests that 150 minutes of exercise per week alone does not result in significant weight loss, the DPP concluded that this amount does prevent diabetes, most likely by increasing insulin sensitivity. Exercise is also a critical element in preventing weight regain after the initial loss. Furthermore, it reduces risk for cardiovascular disease and diabetes beyond that produced by weight loss alone. Therefore, exercise prevails as an essential component of a healthy lifestyle for promoting overall weight loss, weight maintenance, and chronic disease prevention [51].

SPECIFIC EXERCISE RECOMMENDATIONS

Aerobic Exercise

In addition to a healthful diet and modest calorie restriction, the American Diabetes Association recommends a minimum of how much physical activity for the prevention of type 2 diabetes?

As noted, for the prevention of type 2 diabetes, the ADA recommends a minimum of 150 minutes of moderate-to-vigorous intensity aerobic activity per week, along with a healthful diet and modest calorie restriction. Aerobic exercise is defined as "rhythmic, repeated, and continuous movements of the same large muscle groups for at least 10 minutes at a time" [37]. Examples include walking, bicycling, dancing, water aerobics, and many sports [37]. Because the effect of exercise on insulin sensitivity does not last longer than 72 hours, patients will experience the most benefit to blood glucose if aerobic sessions are no more than two days apart [37; 89].

Some public health recommendations suggest that exercise of at least 30 minutes duration is best for cardiovascular health. However, several research studies have indicated that shorter bouts of moderate physical activity that are accumulated toward the daily goal of 30 minutes can be as beneficial as longer periods. This finding has advantages for people who cannot sustain a full 30 minutes of moderate physical activity. Those with a lower level of fitness, who have limited time, or who are low in motivation may be advised to break their physical activity sessions into two or three periods per day of 10 to 15 minutes each [91]. Having this option may make exercise more realistic and appealing to people with certain challenges and barriers to exercise.

While it should be approached as a lifelong commitment, a proper exercise recommendation should include the advice to start gradually and work up to higher intensity. Exercise should also include warm-up and cool-down periods. Warm-up includes 5 to 10 minutes of low-intensity aerobic activity, followed by 5 to 10 minutes of gentle stretching. The cool down should be structured similarly to the warm-up with 5 to 10 minutes of low-intensity movement to bring the heart rate to its pre-exercise level [88].

Determining Exertion Level

Measuring exertion by relative intensity or "how it feels" is an acceptable and often desirable way to know if the activity being done is of appropriate intensity. Measuring relative intensity involves having patients note how the activity affects their breathing and heart rate as opposed to actually taking readings of pulse and respiration. This is desirable because learning to take clinical measures can be complicated for some people and can create a barrier to exercise. One simple way to measure relative intensity of moderate activity is with the "talk test." If a patient is feeling subjective signs of exertion, such as heavy breathing and body warmth, but is still able to talk, but not sing, while engaged in the activity, the intensity of the activity is adequate [92].

The ACSM recommends the use of a "perceived exertion" scale in people with diabetes, other chronic health conditions, and those older than 65 years of age. According to this guideline, moderate-intensity aerobic activity involves, "a moderate level of effort relative to an individual's aerobic fitness" [93]. Using a 10-point scale, whereby sitting is 0 and maximum effort is 10, moderate intensity is 5 or 6 and produces noticeable increases in heart rate and breathing. Vigorous activity is 7 or 8 and produces large increases in heart rate or breathing. Because people have differing levels of fitness, perceived moderate exertion could involve a brisk walk for some or a slower walk for others [89; 93].

While most public health recommendations specify moderate-intensity exercise, the American Heart Association (AHA) and the ACSM include an option for engaging in "vigorous" exercise to meet the exercise target [93]. In particular, for prevention of type 2 diabetes, the AHA recommends 150 minutes per week of "moderate-to-vigorous" physical activity. General recommendations from the ACSM advise 30 minutes of moderate aerobic activity five days per week or vigorous intensity exercise for a minimum of 20 minutes three days per week. Combinations of both exercise intensities may be used to meet this requirement. Vigorous activity is quantified as exertion of 7 or 8 on the perceived exertion scale, along with large increases in heart rate and breathing. Examples of vigorous-intensity exercises include jogging, cross-country skiing, jumping rope, or competitive sports, such as basketball. In helping patients select the intensity of an exercise program, it is important to identify what the individual feels is realistic and feasible, while taking into account age, physical function, and other health conditions.

Resistance Exercise

Experts recommend resistance exercise be a component of the complete fitness program for healthy adults. Resistance exercise is defined as, "activities that use muscular strength to move a weight or work against a resistive load" [37]. Examples include weightlifting, working with resistance bands, and using weight machines.

Resistance exercise increases muscular fitness and improves insulin sensitivity to about the same extent as aerobic exercise. It may also reduce cardiovascular risk factors such as dyslipidemia, insulin resistance, and blood pressure.

Findings on the benefits of resistance exercise to weight management are inconclusive. Some research indicates that resistance exercise is not effective for weight loss, with or without diet restriction [94]. However, other evidence suggests that resistance-training increases muscle mass and enhances body fat loss when combined with calorie restriction. Because muscle weighs more than fat, resistance exercise appears to be beneficial in reducing body fat, if not body weight.

With or without weight loss, increasing muscle mass through resistance exercise may be important in preventing diabetes. A cross-sectional analysis of data on more than 14,000 people suggested that sarcopenia (i.e., reduced muscle mass and strength) was associated with insulin resistance regardless of weight status [95]. Researchers concluded that weight loss alone might not be enough to avert diabetes. It may also be important to have adequate muscle mass and strength, which can be enhanced with resistance exercise [95].

Although there are no specific recommendations for resistance exercise to prevent diabetes, the ADA recommends that people with type 2 diabetes should be encouraged to perform resistance exercise three times per week unless contraindicated. The exercise should include all major muscle groups—legs, hips, back, abdomen, chest, shoulders, and arms. Exercise for each group should progress to three sets of 8 to 10 repetitions. Exercises should be performed to the point at which it would be difficult to do another repetition.

Initial supervision and periodic reassessments by a qualified exercise specialist are recommended to maximize health benefits and prevent injury. Muscle strengthening activities can be done on the same day as aerobic activities or on alternate days. Resistance activities do not count toward the aerobic activity total of 150 minutes per week. The CDC provides resources for getting started with physical activity at https://www.cdc.gov/healthyweight/physical_activity/getting_started.html [96].

Lifestyle Physical Activity

In 2023, the ADA revised its standards of medical care to include a position statement that encourages a reduction in sedentary time (e.g., working at a computer, watching television) for all individuals. Prolonged sitting should be interrupted every 30 minutes for blood glucose benefits [13].

The ACSM states that moderate or vigorous activities of daily living, when performed in bouts of 10 minutes or more, can be counted toward the daily recommendation of approximately 30 minutes total per day. Examples of these types of activities include climbing stairs, gardening with a rake or shovel, and vacuuming. Light activities of daily living, such as shopping and cooking, do not count toward the recommended target for most people, unless the activity produces perceived moderate intensity for the individual [91]. For those who are very sedentary, obese, or otherwise unable to fulfill the daily activity recommendation, any amount of physical activity should be encouraged. A small amount of activity is considered more desirable than none at all. In these cases, patients should be encouraged to take small steps toward increasing physical activity in their daily life in whatever way they can [97].

Pedometers

Step-counting devices can promote increased physical activity in some individuals. Small and inexpensive, the pedometer tracks the number of steps taken per day. A pedometer is most effective if worn all day with attention given to finding opportunities to increase walking throughout the day. A benefit of the pedometer is that it can increase patients' awareness of how much activity they are achieving each day and to motivate them to look for opportunities to be more active, such as taking stairs instead of an elevator. Pedometers are especially useful for people who lack confidence in their ability to exercise, are resistant to a formal program, have been sedentary, have low fitness levels, or have other conditions limiting aerobic activity.

One study demonstrated that sedentary workers who averaged an increase in 3,451 steps per day over a 12-week period showed significant decrease in waist circumference [90]. Another study in England suggested that using a pedometer could reduce diabetes risk by one-half [98]. In this study, people with prediabetes who were given a pedometer and assisted in setting targeted step goals achieved a 15% greater reduction in blood glucose compared to the control group [98].

Achieving 10,000 steps per day is considered an appropriate daily step goal consistent with the recommendation of 30 minutes of moderate-intensity daily activity. If a patient is interested in using a pedometer, advise him or her to begin by wearing it for a full week without altering the usual physical activity level. This will provide a baseline upon which to build. After that time, the patient should gradually increase steps, with a goal of 10,000 steps per day for most people.

HELPING PATIENTS SELECT AN EXERCISE PROGRAM

It is important to guide patients to select a specific exercise plan that meets their abilities and personal preferences. Too often, patients are simply told to "get some exercise" without any support in selecting a specific and appropriate plan. Developing a plan consists of specific recommendations regarding how much activity to engage in, what type of activity, and how and when it will take place. Things to take into account include the patient's individual lifestyle, cultural preferences, current fitness level, physical limitations, social situation, schedule and time commitments, and personal preferences. It may be helpful to begin by asking patients what they are already doing or might like to start doing. This helps identify what they are most motivated to do.

It is also important to help patients select a program that will have the greatest chance for long-term maintenance. The ACSM has identified factors that influence maintenance of exercise behavior [89]:

- Setting realistic goals
- Setting an exercise schedule in advance and sticking to it
- Using an exercise partner
- Encouraging self-rewards
- Identifying alternatives to reduce boredom
- Accepting off days and being able to return to the program after backsliding

Encourage patients to choose activities that are realistic for them. Walking is the preferred form of exercise for most obese patients, but others may prefer swimming or exercise classes. Attainable goals allow patients to experience success and potentially increase morale. Modest initial goals allow for gradual increase in duration and frequency of activity.

Overcoming Barriers

Which strategies can help patients overcome a time barrier to participating in an exercise program?

Educating patients on the benefits of an exercise program and the recommendations for prevention of diabetes can have a significant influence on the decision to implement a plan [89]. However, only one in three patients indicate that they have ever received advice from a healthcare provider to begin or continue to do exercise or physical activity [99].

The best way to educate about the advantages of exercise is to ask patients what they think would be of most benefit to themselves. Most people already know that exercise has many benefits, but it is important for an individual to realize how it can help on a personal level. Patients may cite physical or health benefits as well as psychologic and social rewards. As an educator, expand upon patients' pre-existing knowledge by supplementing and enhancing their list of benefits.

Although most people agree that exercise has many health benefits, only one in six adults have a high level of physical activity [21]. Barriers to exercise can be physical, psychologic, emotional, or situational. Some barriers are perceived, such as a lack of confidence in one's ability to perform, rather than actual.

After barriers to exercise have been identified, steps can be taken to help patients overcome them. For each barrier, ask the patient what he or she thinks could help; this will allow the patient to be actively involved in resolving the barriers. Then, provide suggestions to supplement the patient's problem-solving activity. Common barriers to exercise and suggestions for helping patients overcome them include:

- Not enough time: Strategies may include scheduling time for exercise, walking on lunch break, waking 30 minutes earlier, and/or including exercise in the regular daily routine, such as on the way home from work.
- Too out of shape: Suggest starting slowly and gradually increasing both duration and intensity of exercise. Explore the feasibility of using a pedometer, and reinforce that even a little bit of activity is better than none at all.
- Too tired: Propose exercising at times of day when energy level is higher. Educate that many people feel more energetic overall when they are active on a regular basis.
- Not motivated: Recommend getting social support and/or finding an exercise partner. Ask the patient to identify what would help him or her get and stay motivated. Explore which types of activities would be most appealing.

After patients have examined their personal barriers to exercise, help them explore ideas for activities that meet their interests, lifestyle, and cultural preferences. When patients can visualize themselves performing a behavior and can verbalize their own plan of action and imagine the rewards, they are making genuine movement through the behavior change process.

Personality Traits and Physical Activity

Personality traits contribute to the psychology of physical activity behavior by affecting psychosocial factors (e.g., attitude, beliefs about social pressure, self-efficacy), which influence exercise preferences and adherence strategies. Understanding and identifying the impact of personality traits can help professionals design exercise programs for patients that improve adherence to physical activity [100].

The dominant theory describes a five-factor model that accounts for a majority of individual differences between people based on five personality traits and correlated exercise program considerations [100]:

- Neuroticism (emotionally unstable, anxious, self-conscious): Best suited to exercise that provides short-term, realistic goals. Focus on psychological benefits of regular exercise.
- Extraversion (tends to be sociable, assertive, energetic): Prefers highly social environments (group classes). Emphasize recovery for these individuals who tend to overexert themselves.
- Openness (perceptive, creative, reflective, generous): Prefers outdoor activities that encourage adventure (e.g., hiking, rock climbing). Variety and autonomy in self-selecting exercise improves adherence.
- Agreeableness (kind, cooperative, altruistic, trustworthy): Typically cooperative with exercise programs. May benefit from motivational interviewing to understand exercise preferences.
- Conscientiousness (ordered, dutiful, self-disciplined, achievement oriented): Prefers high-intensity exercise sessions. Good at planning out personal short- and long-term goals. Likely enjoys logging personal performance data.

PHARMACOTHERAPY FOR PATIENTS WITH PREDIABETES

MEDICATIONS TO PREVENT DIABETES

Which medications are approved by the U.S. Food and Drug Administration for the prevention of diabetes?

One arm of the DPP research study examined the efficacy of metformin as a pharmacologic agent to prevent the onset of type 2 diabetes in high-risk people. Results indicated that metformin reduced diabetes onset by 31%, whereas lifestyle intervention reduced the risk for diabetes onset by 58% [2]. Metformin was found to be most effective in younger, more obese patients and showed little benefit for those 60 to 85 years of age [2]. Reviews of more than two decades of clinical use have demonstrated that metformin is generally well-tolerated and safe and beneficial for diabetes prevention among higher-risk patients [101; 102]. It also may be beneficial for patients who are unable to adhere to lifestyle changes [103].

Long-term use of metformin therapy has been associated with vitamin B12 deficiency. The ADA recommends periodic B12 measurement in patients treated with metformin, particularly those with anemia or peripheral neuropathy [13].

As of 2023, no drug is approved by the FDA to prevent diabetes or treat insulin resistance. However, the ADA recommends that metformin therapy be considered for the prevention of diabetes in certain patients, including [13]:

- Those with prediabetes, especially with BMI ≥35
- Those younger than 60 years of age
- Women with prior gestational diabetes

EVIDENCE-BASED PRACTICE RECOMMENDATION

In addition to lifestyle measures, the American Diabetes Association recommends metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially those 25 to 59 years of age with BMI ≥35, higher fasting plasma glucose (e.g., ≥110 mg/dL), and higher A1c (e.g., ≥6.0%), and in individuals with prior gestational diabetes mellitus.

(https://diabetesjournals.org/care/issue/47/Supplement_1. Last accessed January 10, 2024.)

Level of Evidence: A (Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered)

Other antidiabetic medicines have also been studied for their effect on diabetes prevention. Rosiglitazone is an insulin-sensitizing drug that has led to reduced incidence of diabetes in clinical trials, but its long-term effectiveness is not known. Furthermore, clinical trials have not compared the effectiveness of rosiglitazone to lifestyle intervention or other pharmacologic agents. Other evidence suggests that using low-dose combination therapy of metformin and rosiglitazone results in risk reduction for diabetes onset [104]. In July 2010, the FDA reviewed the safety of rosiglitazone based on its potential for cardiovascular side effects. The advisory committee determined that rosiglitazone could remain on the market but with restrictions on its use and additional warnings about the risk for myocardial infarction and congestive heart failure [105]. These restrictions were removed in November 2013 after the FDA determined that data did not demonstrate an increased risk of heart attack with rosiglitazone compared with the standard type 2 diabetes medications metformin and sulfonylurea [106]. Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program the FDA can require for medications with serious safety concerns. In December 2015, the FDA eliminated the REMS for rosiglitazone after a period of continuous monitoring revealed no new pertinent safety issues [107]. Other reported side effects of rosiglitazone include weight gain, bone fracture, and peripheral edema (rare) [105].

The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial reported that three years of therapy with rosiglitazone reduced the primary outcome of diabetes or death by 60% [108]. A passive follow-up study (DREAM On) investigated whether diabetes prevention persisted more than 1.5 years after discontinuation of therapy [108]. Consenting participants had repeat OGTT one to two years after therapy ended. A diagnosis of diabetes was based on either a fasting glucose level of ≥7.0 mmol/L, or a two-hour plasma glucose level of ≥11.1 mmol/L), or a confirmed diagnosis by a physician not involved in the study. Regression to normal blood glucose was defined as a fasting glucose level of <6.1 mmol/L or a 2-hour plasma glucose level of <7.8 mmol/L. After a median of 1.6 years post-trial, the rosiglitazone participants had a 39% lower incidence of diabetes or death and 17% more regression to normal blood glucose. Similar incidences of the primary outcome and regression were observed in participants from both the ramipril and rosiglitazone groups. Ramipril did not have any significant long-term effect. Rosiglitazone reduced the longer term incidence of diabetes by delaying, but not reversing, the underlying disease process [108].

Another drug, acarbose, was found to reduce the progression of IGT to type 2 diabetes by 25% over 3.3 years in one study [109]. Because this medication can cause significant gastrointestinal side effects, many subjects discontinued the study medication [105]. This raises questions about the efficacy and practicality of using acarbose to prevent type 2 diabetes in actual clinical practice [109].

A review of eight randomized controlled trials investigated the effects of acarbose in people with IGT, IFG, moderately elevated A_{1c}, or any combination of these [110]. Trial duration ranged from one to six years, and most trials compared acarbose with placebo. Of 4,014 participants who received acarbose, 670 (16.7%) developed diabetes; of 3,994 participants who received placebo, 812 (20.3%) developed diabetes. When acarbose was compared with no intervention, 7 of 75 participants (9%) who received acarbose developed type 2 diabetes, compared with 18 of 65 participants (28%) who received no intervention. Treatment with acarbose neither reduced nor increased the risk of death from any cause, death from heart disease, serious side effects, stroke, or heart failure [110].

MEDICATIONS TO PROMOTE WEIGHT LOSS

Agents approved for weight loss have been shown to decrease the incidence of diabetes in those with prediabetes [111; 112]. However, as stated, none are FDA-approved for diabetes prevention [13]. There are five medications (orlistat, phentermine/topiramate, bupropion/naltrexone, semaglutide, and liraglutide) approved by the FDA for the long-term treatment of obesity [110]. These medications have been shown to be modestly effective in promoting initial weight loss, with improved results when used in combination with lifestyle changes [110; 113]. Another medication, lorcaserin, was withdrawn from the U.S. market in February 2020 [105; 110].

Orlistat is available by prescription (as Xenical) or over-the-counter in half-strength under the brand name Alli. It acts by deactivating gastric and pancreatic enzymes, thus preventing the absorption of fat through the gastrointestinal wall [110]. Gastrointestinal side effects, such as bloating, gas, and oily stools, account for a high rate of discontinuation.

Phentermine/topiramate (extended-release) combines an anorexiant and an anticonvulsant to improve short-term weight-loss outcomes in patients who have already attempted lifestyle changes (i.e., calorie-restricted diet and increased physical activity) [105]. Eligible patients will have a BMI ≥30 or a BMI ≥27 with a weight-related comorbidity [105]. The medication is contraindicated in persons with glaucoma and hyperthyroidism and is not recommended for patients with a recent history of stroke or heart disease [105]. It is also teratogenic, with proven fetal defects with first trimester exposure. Therefore, all women of childbearing age should use effective contraception consistently while taking the drug and have documented proof of a negative pregnancy test prior to the initiation of treatment and every month thereafter [105].

Bupropion/naltrexone is approved as a treatment option for chronic weight management in conjunction with a reduced-calorie diet and increased physical activity [105]. As with phentermine/topiramate, eligible patients will have a BMI ≥30 or a BMI ≥27 with a weight-related comorbidity [105]. The dosage is gradually titrated up, starting with one tablet (naltrexone 8 mg/bupropion 90 mg) once daily in the morning for one week and increasing one daily tablet each week for four weeks. The maintenance dose is two tablets twice daily [105]. If 5% of initial body weight has not been lost after 12 weeks, the medication should be discontinued [105]. Any patient taking bupropion should be carefully monitored for suicidal ideation and behaviors [105]. This medication may also increase blood pressure and heart rate and is contraindicated in patients with hypertension. It is also contraindicated in patients with a history of seizures, who are taking another bupropion-containing medication, or who are pregnant [105].

The GLP-1 receptor agonist liraglutide also is approved by the FDA for chronic weight management. Traditionally used to treat diabetes, liraglutide has been found to aid in appetite suppression and weight loss [114]. Eligible patients will have a BMI ≥30 or a BMI ≥27 with a weight-related comorbidity [105]. The dosage of liraglutide used for weight management (3 mg) differs from the dose used in diabetes medication regimens (1.8 mg), and the safety and efficacy of this higher dose for the treatment of diabetes has not been established [114]. If 5% of initial body weight has not been lost after 12 weeks, the medication should be discontinued [105]. This medication is contraindicated in pregnant women and in those with a personal or family history of thyroid cancer [105; 110].

In 2021, the FDA approved semaglutide injection for chronic weight management in adults with obesity (BMI ≥30) or overweight (BMI ≥27) with at least one weight-related condition (e.g., hypertension, type 2 diabetes, hyperlipidemia) [115]. This agent is a glucagon-like peptide-1 (GLP-1) receptor agonist and is intended to be used in conjunction with lifestyle changes. When used for weight management, semaglutide is administered subdermally at a dose of 2.4 mg once weekly [115].

In addition, setmelanotide injection, a melanocortin 4 receptor agonist, is approved for use in cases of rare genetic mutations resulting in severe hyperphagia and extreme obesity [13; 110].

Tirzepatide was approved for type 2 diabetes treatment by the FDA (as Mounjaro) in 2022 [105]. In 2023, the FDA also approved the agent for chronic weight management, with the same indications as semaglutide [105]. Tirzepatide acts as a dual incretin agonist of GLP-1 receptor and glucose-dependent insulinotropic polypeptide (GIP) receptor and is dubbed the "twincretin" [105]. The initial dose is 2.5-mg subcutaneous injection once weekly for four weeks, at which point it is increased to 5 mg once weekly. Further dose escalation in 2.5-mg/week increments (up to a maximum weekly dose of 15 mg/week) is possible every four weeks [105].

METABOLIC SURGERY

In a 2010 study, what percentage of gastric banding patients with type 2 diabetes experienced a return to normal glycemia after the procedure?

Reviews and meta-analyses of publications concerning metabolic surgery have consistently found improvement or resolution of diabetes in the majority of patients. A 2010 study demonstrated that gastric banding surgery could induce a remission of existing type 2 diabetes, with 73% of the study group returning to normal glycemia. Another study indicated that gastric banding induced prolonged satiety and resulted in improved glycemic control. Of those who did not achieve euglycemia, glycemic control was improved [109]. This suggests that surgical intervention may be an appropriate approach for preventing diabetes in select patients who are unable to lose weight by other means. The ADA recommends metabolic surgery as an option to treat type 2 diabetes in screened surgical candidates with a BMI of 40 or greater (37.5 or greater in Asian Americans) and in adults with a BMI of 35.0–39.0 (32.5–37.4 in Asian Americans) who have type 2 diabetes and who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods [13]. Metabolic surgery may be considered as an option for adults with diabetes and BMI 30.0–34.9 (27.5–32.4 in Asian Americans) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with tested efficacious nonsurgical methods [13]. After metabolic surgery, patients must receive ongoing lifestyle support and monitoring of micronutrient and nutritional status [13].

PREVENTING DIABETES IN CHILDREN

The Centers for Disease Control and Prevention recommend that children and adolescents participate in how much daily physical activity?

The incidence of childhood obesity has more than tripled since the 1970s [116]. Obesity and type 2 diabetes are parallel epidemics in the United States, as these problems stem from a culture of calorie-dense foods, excess sugar consumption, and sedentary lifestyle. This has resulted in increasing rates of type 2 diabetes in youth, which was a very rare condition in past generations. Cultural and lifestyle changes over the last few decades may have even caused genetic mutations that decrease insulin sensitivity in the current generation of American children [116].

The potential burden of type 2 diabetes in children is immense. Because earlier onset of diabetes heralds longer duration and severity of its complications, this jeopardizes fiscal resources and has the potential to diminish the productivity and quality of many young lives. Keeping children at a healthy body weight appears to have lifelong effects on their mortality. Evidence suggests that obesity and glucose intolerance in children are strongly associated with increased rates of premature death [117; 118]. Young men who are obese at 20 years of age have double the risk of dying prematurely, an effect that lasts for decades. Furthermore, the chance of early death in this population increases by 10% for each BMI point greater than 25 [117]. Obesity also increases the risk for nonalcoholic fatty liver disease in children, a condition associated with insulin resistance [118].

While the estimated number of children with prediabetes is not available, one in 5 adolescents in the United States is obese; because body fat is the strongest predictor of insulin resistance in children, it is estimated that many of these children also have some level of prediabetes [116]. Puberty aggravates the risk for diabetes onset in youth due to normal biologic changes that increase insulin resistance. Children who are overweight or obese during adolescence face an even greater risk of developing type 2 diabetes.

In addition to obesity, risk factors for childhood type 2 diabetes include family history, having a birth mother with gestational diabetes and/or who did not breastfeed, and African American, Native American, or Hispanic ancestry.

More research is necessary to determine how to address prediabetes in children. It is unknown whether children with prediabetes have the same degree of risk for developing type 2 diabetes as adults with prediabetes, or if the predictors for long-term risks of diabetes are the same for children [119; 120]. The ADA recommends that risk-based screening for prediabetes and/or type 2 diabetes be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents with overweight (BMI 85th percentile or greater) or obesity (BMI 95th percentile or greater) and who have one or more of the following risk factors for diabetes [13]:

- Maternal history of diabetes or gestational diabetes during the child's gestation
- Family history of type 2 diabetes in first- or second-degree relative
- Race/ethnicity (e.g., Native American, African American, Latino, Asian American, Pacific Islander)
- Signs of insulin resistance or conditions associated with insulin resistance (i.e., acanthosis nigricans, hypertension, dyslipidemia, PCOS, or small-for-gestational-age birth weight)

EVIDENCE-BASED PRACTICE RECOMMENDATION

The U.S. Preventive Services Task Force recommends that clinicians screen for obesity in children and adolescents 6 years and older and offer or refer them to comprehensive, intensive behavioral interventions to promote improvements in weight status.

(https://www.uspreventiveservicestaskforce.org/uspstf/document/RecommendationStatementFinal/obesity-in-children-and-adolescents-screening. Last accessed January 10, 2024.)

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

Children may be the best targets in efforts to curb the trend toward obesity and type 2 diabetes in the United States, as habits and lifestyle may be easier to change in early life, before they become firmly established. Curbing childhood overweight and obesity starts with the family environment; good family eating and exercise habits promote healthy weight in the children. Families who eat home-cooked meals on a regular basis are more likely to produce leaner children [121]. When encouraging families to adopt more appropriate eating habits, avoid using the term "diet," but instead talk about changing to a "healthy lifestyle." Tips for families adopting healthier eating habits include:

- Check online resources that are designed to help children learn about good health habits in a fun, interactive way.
- Eliminate junk food in the house.
- Modify family recipes to be healthier, such as substituting lean ground turkey for hamburger and baking foods rather than frying.
- Add more vegetables to soups, stews, and casseroles.
- Involve children in the preparation of healthy family meals.
- Do not serve a special meal to a child who does not want to eat the food served at the family meal.
- Turn off the television, radio, and music during the family meal. Focus on conversation and family interaction.
- Have children eat breakfast every day. Serve whole-grain cereals with 5 grams or less of sugar per serving. Other good choices for a healthy, child-friendly breakfast include whole-grain frozen waffles, oatmeal, and low-fat yogurt with fresh fruit.

- Healthy sack lunch ideas include sandwiches on whole grain-bread, fruits and vegetables, tuna fish, and lean sandwich meats.

The CDC recommends that children and adolescents participate in at least 60 minutes of physical activity every day [122]. A study presented at the 2010 ADA annual meeting revealed that obese boys who engaged in aerobic and resistance exercise decreased their total body fat, visceral fat, and insulin resistance, even without any changes in diet [123]. The study also indicated that resistance exercise training is appealing to boys and that it expends similar energy to aerobic training in this population.

Aerobic exercise should make up most of the 60 minutes of the daily exercise. This should include vigorous-intensity exercise at least three days per week. Children should have muscle-strengthening exercise at least three days per week as part of their 60 minutes per day. This could include push-ups and climbing on playground equipment. Bone-strengthening exercise is recommended three days per week, included in the 60 minutes per day requirement. Bone strengthening exercises include weight-bearing exercise such as jumping rope and running [122].

Today's generation of children have more opportunity to be entertained by sedentary activities, such as television, computers, movies, and electronic games, than by active play. Screen time is correlated with obesity and poor dietary habits in children and with clinical markers for metabolic syndrome and cardiovascular disease in adults. A 2010 study showed that teenage boys with two or more hours per day of television or computer screen time are at greater risk for insulin resistance and other markers of metabolic syndrome [124].

Tips for the family working to become more active include:

- Limit television, computer, or game "screen time" to less than two hours per day.
- Assign children to active chores, such as raking leaves or carrying grocery bags.
- Have children walk or ride their bikes to school when possible.
- Have active family outings, such as walks, ball games, and swimming.
- Encourage sports. If the child is not competitive, look for team activities that focus on fun and participation rather than winning.
- Parents can be good roles models by being active themselves.

Clinic-based weight management programs appear to be effective in improving the metabolic profile of obese children, if they remain in a supervised program for several years. Results of a pilot program in Philadelphia suggest that an informal, nonintensive program of regular clinician contacts over two years can be more effective than intensive time-limited programs [125]. In this study, the greatest improvements in children's metabolic profile correlated with frequency of visits to the healthcare provider [125].

PUBLIC HEALTH INITIATIVES

On a broader level, a public health approach to fighting childhood obesity is needed. This should include school programs that integrate nutrition, physical education, and sociobehavioral approaches to promote healthy lifestyle choices among youth. School lunch programs should offer healthy choices and strictly limit foods that are high in fat and sugar from cafeterias, food courts, and vending machines. School-based exercise programs are also very important in promoting the health of children. Because working parents may not have time to exercise with their children and many children do not live where it is safe to play outside without adult supervision, children need the opportunity for physical activity during the school day.

The battle against childhood obesity should extend beyond the school into the broader public health sector. Public health education should be family-centered and provide children with knowledge and avenues for behavioral change. These educational approaches should be multicultural in nature, taking into account the various health beliefs and dietary patterns of the populations directly affected by current rates of obesity and diabetes. Information about state and local programs focused on promoting health efforts are available on the CDC website at https://www.cdc.gov/nccdphp/dnpao/state-local-programs/index.html.

ETHNIC VARIABILITY AND CULTURAL CONSIDERATIONS

Culture greatly influences patients' belief systems and values related to health and lifestyle. Culturally sensitive diabetes education programs are effective in reducing A_{1c}, total and low-density lipoprotein (LDL) cholesterol, and microalbumin [121].

Culturally competent care is defined as "effective individualized care that demonstrates respect for the dignity, personal rights, preferences, beliefs, and practices of the person receiving care, while acknowledging the biases of the caregiver and preventing these biases from interfering with the care provided" [126].

Cultural competency involves practicing cultural humility, which consists of recognizing the differences and limitations of one's own culture when working with people of other cultures. Practicing cultural humility requires striving to overcome cultural biases and the barriers they may present. Cultural humility reduces the likelihood of authoritative communication from the healthcare provider. Even if education and experience have given one a good understanding of another culture, cultural humility means not assuming to know what it is like to be born of and live that culture every day [127]. Perhaps more than any other construct, culture influences a person's food choices, exercise preferences, and eating behavior. Cultural dietary preferences, meal preparation practices, and the symbolism of food represent important aspects of an individualized plan of care. When discussing diet, consider the food preferences of the patient's cultural group, and keep in mind that contact with the mainstream culture may have influenced these preferences [128]. Also keep in mind that each cultural group is large and diverse; there is no single common diet for each group. Creating an intervention for Latin Americans/Hispanics or African Americans may be differentially effective for the group's specific subpopulations [129].

Oldways is a nonprofit organization dedicated to helping people eat healthy, plant-based diets that maintain traditional preferences and practices. This group provides several multicultural food pyramids and science-based information about traditional diets online at https://oldwayspt.org [130].

LATIN AMERICANS/HISPANICS

What foods are part of a traditional Hispanic diet?

Diabetes is an urgent issue in the Latin American/Hispanic communities. Hispanic adults are 70% more likely than non-Hispanic White adults to be diagnosed with diabetes [131]. Rates of complications of diabetes are also higher among this group. Abdominal obesity and insulin resistance greatly increase the risk for metabolic syndrome in this population.

In Latin American/Hispanic cultures, the family unit is very important and the needs of the family are placed above the needs of the individual. Winning *confianza* is important in establishing the nurse-patient relationship. This is achieved by showing respect for the culture and willingness to engage in non-healthcare-related conversation with the patient. A warm, caring, and personable manner is valued. Latino/a clients may perceive a neutral attitude from the healthcare provider as a negative attitude. This population tends to prefer teaching methods that involve storytelling and other audio presentations to printed materials [127].

The traditional Hispanic diet is high in fruits, vegetables, and fiber, and low in fat. However, acculturation to the American diet has changed traditional preferences and practices to a less healthy style of eating. Healthy choices most likely to appeal to this population include [128]:

- Vegetables: Cabbage, carrots, cassava, jicama, nopales, peppers, tomatoes (salsa)
- Fruits: Açaí, agave, banana, cherimoya, guava, mango, passion fruit, starfruit
- Grain/starch: Amaranth, bread, corn, pasta, quinoa, rice, tortilla
- Legumes, nuts, seeds: Pine nuts, black, garbanzo, kidney, and pinto beans
- Protein: Abalone, crab, sea bass, cod, chicken, eggs, beef, pork
- Dairy: Asadero cheese, yogurt, milk

According to data from the CDC, 49.5% of Hispanic Americans are physically inactive, compared with 38.9% of White Americans [132]. A small study of Hispanics has suggested that a group-dancing program is a culturally appealing form of exercise among Mexican Americans [133].

AFRICAN AMERICANS

Diabetes strikes 1 out of every 13 Black Americans, and about one-third of these individuals are unaware they have the disease [134]. African Americans with diabetes are more likely to develop serious long-term complications and suffer greater associated disability than other racial/ethnic groups [134]. Genetic predisposition plays a major role in the higher incidence of IGT and diabetes in African Americans. As for body type, African Americans have a greater tendency for upper-body or central obesity, which is a known risk factor for metabolic syndrome.

African Americans have a high prevalence of cardiovascular risk factors that may be reduced with lifestyle modification. These include obesity, hypertension, sedentary lifestyle, and tobacco use [127]. Unfortunately, studies have indicated that African Americans are less likely to participate in health screening programs. This is due in part to poor access, but may also stem from cultural and historical factors, such as mistrust of the healthcare system stemming from a history of inequitable treatment [127].

Studies have been performed to determine the best way to help African Americans make lifestyle changes for preventive health. One study concluded that being involved in group support and education sessions to promote weight loss was not effective for this population. This same study also showed that keeping food diaries did not help African American patients lose weight [78]. These findings suggest that alternate approaches to weight loss should be considered when working with African American patients.

Traditional food preferences of African Americans are regional, and many White Americans in the southern United States share these food preferences. They include [128]:

- Vegetables: Kale, spinach, collard, mustard, turnip, and dandelion greens

- Grains/starch: Corn, cornbread, yeast rolls, sweet and white potato, rice with black-eyed peas ("hoppin' John"), succotash (corn with lima beans), rice, grits
- Legumes: Field peas, green peas, pinto, navy, butter, and lima beans
- Protein: Beef and pork, poultry, fish
- Dairy: Traditionally whole milk, but 2% and nonfat milk are becoming more popular

ASIAN AMERICANS/PACIFIC ISLANDERS

This group encompasses people from a wide geographic area, consisting of many different subcultures. However, there are a few similarities in food preferences and cultural traditions that tend to occur across these cultures.

The incidence of diabetes among Asian Americans has increased more rapidly among those who have lived in the United States for a longer period of time than among new immigrants or those living in Asia [127]. Japanese individuals living in Seattle have diabetes prevalence four to five times that of those living in Tokyo [127]. Use of BMI is not as reliable a tool for predicting diabetes risk in Asian populations, as they tend to develop insulin resistance and type 2 diabetes at much lower indices [13; 135]. The International Diabetes Federation has determined lower measures of waist circumference for determining health risk in Asian populations [135]. A systematic review of dietary self-management of diabetes among Asian Americans identified themes, including cultural beliefs about food, that characterize the cultural perspectives and experiences that influence diabetes self-management [136]. Patients reported receiving dietary recommendations that did not align with their beliefs about food as medicine and a source of balance in life and that recommendations to remove refined carbohydrates (e.g., rice) from their diets caused them to feel isolated from familiar and shared food habits and practices [136].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Diabetes Association recommends a lower body mass index cut point (23 rather than 25) for screening overweight or obese Asian Americans for prediabetes and type 2 diabetes to reflect the evidence that this population is at an increased risk for diabetes at lower BMI levels relative to the general population.

(https://diabetesjournals.org/care/issue/47/Supplement_1. Last accessed January 10, 2024.)

Level of Evidence: B (Supportive evidence from well-conducted cohort and/or case-control studies)

In general, white rice is a basic and important component of Asian diets. Virtually every Asian meal includes white rice, accounting for up to 75% of the diet [137]. Because greater consumption of white rice is associated with higher risk for diabetes and can significantly raise blood glucose in people with diabetes, this cultural preference, as stated, presents a significant challenge for many. A review of four studies involving more than 352,000 people from China, Japan, the United States, and Australia found that people who ate three to four servings of white rice daily were 1.5 times more likely to have diabetes than those who ate the least amount of rice. For every additional large bowl of white rice a person ate each day, the risk rose 10%. The link was found to be stronger for people in Asian countries, who eat an average of three to four servings of white rice per day [138]. In contrast, a brown rice intake of two or more servings per week has been associated with a lower risk of diabetes, supporting the recommendation that most carbohydrate intake should come from whole grains [139].

Traditional Asian food preferences include:

- Vegetables: Carrots, broccoli, mushrooms, bok choy, cabbage, bamboo shoots, chilies, bean sprouts, scallions, leafy greens
- Fruits: Pineapple, banana, mango, tangerine, watermelon, grapes, pear
- Grains/starch: Rice, noodles
- Protein: Soybeans, tofu, fish, shellfish, egg, poultry, beef, pork

From a cultural standpoint, many Asian cultures do not value strenuous physical activity, focusing instead on martial arts and tai chi. Family values influence childhood participation in organized sports and overall physical activities, which in turn shapes the role of exercise in the management of diabetes [140]. Additional research is necessary to determine an appropriate, yet culturally sensitive, exercise intervention strategy for this population [141].

ASIAN INDIANS

Dietary practices among Asian Indians vary according to region of origin within India and the form of religion practiced. For many Asian Indians living in the United States, the traditional low-fat, high-fiber diet has evolved to include more saturated fat and fast food. Traditional dietary preferences include:

- Vegetables: Spinach, tomato, cauliflower, okra
- Fruits: Banana
- Grains/starch: Rice, chapati (a flat bread), lentils, whole-grain bread, potato
- Legumes: Peas, kidney beans
- Protein: Fish, poultry, nuts
- Dairy: Yogurt, paneer (a semi-firm cheese)

AMERICAN INDIAN/ALASKA NATIVES

Native Americans are a diverse population, representing several hundred different groups that have settled on the North American continent. In addition, there are Alaska Natives who are distinct from Indian tribes of the continental United States. Many Native Americans live on reservations in rural areas, but just as many live in urban areas. Because each tribe has a unique history, geographic location, social system, cultural styles, and traditions, only general aspects of this group are presented here.

American Indian/Alaska Native adults are almost three times more likely than non-Hispanic White adults to be diagnosed with diabetes and 2.3 times more likely to die from diabetes [142]. The highest rates of diabetes are reported among the Pima Indians of Arizona, where 50% of the adult population has diabetes [143]. Genetic predisposition along with modernization and dietary changes are responsible for the increased rate of diabetes among this population.

In general, Native Americans may not be comfortable disclosing personal information, especially to an outsider. Having a "problem" may be perceived as placing oneself lower on the rung of power. Using an aggressive approach to problem-solving during the healthcare encounter can damage the relationship. Appropriate teaching methods for this population include one-to-one instruction using demonstrations, pictures, and other visuals.

Food is an important part of most Native American cultures and is used in many cultural rituals, spiritual ceremonies, and social activities. The traditional diet was very healthy, but poverty and modernization have led to more reliance on foods such as lard, sugar, and white flour.

Traditional food preferences of Native Americans depend upon geographic location and may include:

- Vegetables: Nopales (cactus), squash, carrots
- Fruits: Strawberries, grapes, oranges, apples, melons
- Grains/starch: Corn, rice, wild rice, wheat, oats, beans, deep fried bread (fry bread)
- Legumes: Nuts, acorns
- Protein: Beans, wild game, fish, beef

BEHAVIOR CHANGE

Although convincing research results tell us that diabetes is preventable with lifestyle modification, many patients face considerable challenges in putting these recommendations into action. For example [144; 145]:

- Only 1 in 33 people are at healthy weight, nonsmoking, physically active, and consume five or more fruits and vegetables per day.
- Only 1 in 3 people with prediabetes are taking steps to prevent diabetes.
- Only 1 in 6 people have a high level of physical activity.
- Two of every five people with type 2 diabetes skip breakfast.
- Americans average 16 grams of fiber per day, while the recommended minimum is 20 to 35 grams per day.
- Sixty percent of people with diabetes do not follow medical advice on how to manage their condition.

Clearly, health behavior change presents a dilemma for individuals, healthcare providers, and the public health sector. Healthcare providers often report feeling frustrated and challenged by patients who do not follow their advice. It is apparent that, in addition to providing recommendations, healthcare professionals also need to facilitate patients' behavior change process.

HEALTH BELIEF MODEL

The Health Belief Model (HBM) provides the basis for widely used strategies that assist patients in making health behavior change [146]. Originally developed in the 1950s, the HBM has been expanded and increasingly popularized over the past two decades. Based on psychologic theory, the HBM examines factors that motivate people to change health behaviors and strives to understand what makes them take action to prevent or manage illness.

Perceived susceptibility is the first construct of the HBM. This may be reflected by the patient considering "What is the likelihood that I will get diabetes?" Patients who believe the risk is low will be less likely to make changes to prevent diabetes. Educating patients about the risk factors for diabetes will help them understand their susceptibility.

Perceived severity refers to how serious a patient believes the condition to be. Patients may consider how diabetes could affect their health, quality life, and functional ability. Of all of the constructs of the HBM, perceived severity has been found to be the least powerful predictor of behavior change.

Perceived benefits refer to a patient's belief about the advantages of taking action. For example, in addition to recognizing the health benefits of weight loss, a patient may also expect it to bring psychologic, emotional, and social benefits. Patients may be motivated to make change by stating the benefits they perceive weight loss would bring and having these reflected back to them.

Perceived barriers are the perceived negative aspects of behavior change; these are things that may impede change. A patient may feel that healthy eating is too complicated and boring. Exploring barriers and ways to overcome them are an important part of the behavior change process.

Cues to action are the "wake-up call" that prompts a patient to seek change. A call from the doctor reporting elevated blood glucose may give a patient a reason to think about changing his or her eating habits. Readiness is an important part of the behavior change process. It is important to explore the degree of readiness that patients have and learn appropriate responses to their self-identified level of readiness. These strategies will be discussed in detail later in this course.

Self-efficacy refers to a person's sense of confidence in his or her own ability to perform a behavior or a set of behaviors. Theoretically, people who are confident that they will be successful are more likely to perform that behavior. A patient's confidence can be boosted with a statement such as, "From what you have told me, I feel that you will be able to make a plan that will work for you."

Assessment of patients' self-efficacy involves asking them how confident they are that they can make the change. If confidence is low, ask them what it would take to make them feel more confident. It is important to negotiate realistic goals and an action plan with which your patient feels confident. Being able to meet a goal increases self-efficacy. If goals and action plans are not achievable, help the patient modify them to become more realistic.

ROLE OF THE HEALTHCARE PROVIDER IN BEHAVIOR CHANGE

What are the components of the U.S. Preventive Services Task Force's Five A's protocol?

The healthcare professional's role in helping patients change behaviors to prevent diabetes should not be underestimated. Even simply providing evidence-based advice and culturally sensitive education can result in modest changes in health behaviors, such as those related to diet modification and tobacco cessation. However, patients who passively receive education and advice are not as likely to make lasting behavior change as are those who actively participate in the process of change. Effective intervention to support behavior change usually requires multiple encounters that include more than just passively receiving advice. Patients must learn how to translate awareness into plans, and plans into action. There are several effective strategies for helping them do this.

The U.S. Preventive Services Task Force has developed the Five A's protocol, a widely used framework for supporting behavior change in clinical settings [147]. The Five A's protocol can help structure an approach to help patients make health behavior changes. The Five A's are [147]:

- Assess current practices, barriers, and readiness to change.
- Advise patient about what to change.
- Agree on patient goals (negotiate).
- Assist with change strategies and overcoming barriers.
- Arrange for resources and referral, follow-up, and support.

Collaborative Relationship

The most effective relationship for supporting behavior change is one that is collaborative. Collaboration involves mutual agreement upon an agenda, focusing on the patients' goals, and understanding their points of view. Healthcare professionals will be more effective change agents if they take opportunities to help patients identify and address their own problems rather than always giving advice. Helpful communication strategies for building a collaborative relationship include [148]:

- Asking open-ended questions (e.g., What do you think is the most important thing for you to work on today?)
- Using reflection (e.g., You find it hard to keep from eating while watching television in the evening.)
- Summarize patients' general ideas (e.g., I hear you saying that certain habits might be hard to give up, but that you would really like to eat more healthfully.)

Patient empowerment assumes that the patient is the person having the primary rights and responsibilities associated with his or her own health and lifestyle. It emphasizes the patient's role in decision making. Therefore, the goal of education is to provide the information patients will need for successful management of their own care. According to the empowerment model, educators are most effective if they recognize that they cannot and should not try to solve patients' problems for them. Instead, it is vital to provide the education patients need in order to make informed decisions and to facilitate their own decision-making process. This involves assessing readiness to change and exploring the range of options available and the consequences of each.

Providing Sensitive Care to Obese Patients

The National Weight Control Registry advises that serious long-term commitment to lifestyle changes in eating and physical activity is a key to weight loss success in obese patients [149]. Obesity can present significant psychosocial challenges for a person, including discrimination in work, social, and even healthcare settings.

Some obese patients will feel that they are treated insensitively or with judgment, including feeling shame and stigmatization in the healthcare setting. Obese patients report feeling blamed for personal failure and being simply told to lose weight without receiving any tangible support [150]. At the same time, physicians and other members of the healthcare team may be uncomfortable managing obesity. Research shows that healthcare providers often feel unprepared to help patients with behavior change [151]. In fact, patients are less likely to receive weight management advice from their physicians than they are from family and friends [150].

A study of the attitudes and opinions of obese adults in Australia found that this population prefers weight-loss interventions that are designed to help them improve their overall lifestyle, rather than just focusing on weight loss [152]. Public health interventions and media campaigns were favored over commercial weight-loss programs in this group. Furthermore, about 65% of participants felt that regulation, such as banning junk food advertising, was needed to help solve the obesity problem [152].

Stigmatization may be subtle and unintended by the healthcare provider. When working with an obese population, it is important to evaluate personal biases and examine how they may unintentionally affect your patients. Explore assumptions about body weight and dispel these stereotypes. Appropriate care of obese patients requires adopting sensitive language that enhances the therapeutic relationship. Studies show that obese patients prefer words like "weight," "excess weight," or "body mass index" as opposed to "large size," "weight problem," or "unhealthy body weight" [150].

STAGES OF CHANGE

Losing weight, eating differently, and increasing exercise are significant behavior changes for many people with prediabetes. Although it is tempting to think of change as a discrete event, it is actually an unfolding process that happens over time. "Stages of change" refers to the theory that people move through a predictable, though not always linear, series of stages as they give up unhealthy behaviors and replace them with health-enhancing behaviors. James Prochaska's Transtheoretical Model of Behavior Change, which has been widely used in diabetes self-management and smoking cessation, describes the stages of behavior change [153; 154]. Prochaska identified six stages that people go through as they attempt behavioral lifestyle changes, from precontemplation, during which the person does not intend to change within the next six months, to maintenance, when healthy behaviors have been practiced for at least six months. For each stage of change, certain interventions on the part of the healthcare provider are recommended [153].

Precontemplation (Not Ready)

Precontemplation represents a time of resistance to change and may be accompanied by denial that there is a problem or that there would be benefits to change. A patient in this stage resists change and avoids learning or talking about his or her high-risk behavior. This patient is often labeled "noncompliant." In some cases, patients in the precontemplation stage may feel powerless to change. They may say they tried before but failed. It is important to remind these patients that change is a process and relapse is an opportunity to learn about what does and does not work.

For patients who are in the precontemplation stage of change, it is best to remain nonjudgmental and find neutral ways to raise awareness of the problem. When providing objective information, it should be based on caring and concern and not as proof for an argument. Make an effort to establish rapport by listening to the patient with compassion and empathy. Avoid the temptation to argue with the patient. Instead, acknowledge the choice and leave the door open for continued discussion in the future.

Contemplation (Getting Ready)

The contemplation stage begins when a patient becomes less resistant to the idea of behavior change. However, he or she remains acutely ambivalent about change and continues to procrastinate. At this time, the person acknowledges the need for change but is held back by his or her reasons for staying the same. A typical contemplative statement would be, "I would really like to exercise, but I just don't have the time." Although the prospect of change within the next six months is characteristic of this stage, people can remain in contemplation for an extended period of time. Patients may be assisted through this stage by promoting their self-efficacy and supporting their efforts to gather information. Specific interventions include reflective listening, providing empathic feedback, and offering information and resources as appropriate. Motivational interviewing, to be discussed in more detail later, is a powerful method for helping precontemplative and contemplative people move further along in the process of change.

Preparation (Ready)

Preparation is the third stage of behavior change. In this stage, the patient is ready to take action within the next 30 days and may begin to visualize the change. Strategies for this stage are to set goals and formulate an action plan. The healthcare professional's role is to guide the patient in making realistic goals, provide encouragement, offer resources, and help manage anxiety.

Action

During the action stage, the patient demonstrates a strong commitment to change by modifying his or her behaviors and environment. For example, the person who wants to lose weight may begin removing fattening foods from the home. He or she may begin substituting alternative behaviors for the unhealthy habits, such as packing a healthy lunch instead of depending upon fast food. Support from others during this time is very important and will help strengthen the patient's commitment to change and assist with problem solving.

Maintenance

Maintenance is the stage in which patients have maintained desired behaviors for more than six months. During maintenance, patients continue to work to prevent relapse, but their confidence in continuing the new behavior is increased. The new behaviors have become more habitual, and the patient is less conscious of making an effort to perform them. Research indicates that the maintenance stage lasts from six months to five years [153]. During the maintenance stage, healthcare providers can support continued commitment to the behavior, providing feedback on positive changes in clinical measures such as blood pressure, blood glucose, and cholesterol.

Termination

Termination refers to the time when the patient has no temptation to relapse and is completely self-sufficient in maintaining the status quo; the new behavior has become automatic. Long-term abstinence from smoking and drinking alcohol are examples of behaviors that best represent the termination stage of change. For areas like exercise and weight control, complete termination may not be a realistic goal for most people. In these situations, striving for ongoing maintenance is probably more appropriate [153; 154].

Dealing with Relapse

Relapse may occur at any stage of change and can result in a return to the earlier stages. Relapse is a learning opportunity for the patient and should not be viewed as failure. Instead, patients should be encouraged to view it as part of the ongoing process of growth. If a patient has relapsed, be careful to avoid showing feelings of disappointment or chagrin. Instead, help the patient explore the triggers that led to the relapse. Ask how he or she can respond differently to those triggers next time. This is an opportunity to build self-efficacy for another attempt at lasting change.

GOAL SETTING AND ACTION PLANNING

If patients need to lose weight, eat differently, and/or exercise more and they are ready to make these changes, be prepared to help them formulate a realistic plan for accomplishing this. Having specific goals increases the likelihood of performing a behavior and is associated with improved health-related behavior. Successful preventive health care requires a collaborative approach to choosing behavior change goals and identifying the steps to achievement. Start the goal-setting process by asking patients what they would like to start doing to improve their health [155].

Goals vs. Action Plans

A goal has a more generalized outcome that takes place over an intermediate or long-term period, while action plans are highly specific. Examples of goals are:

- I will eat more healthfully.
- I will lose 10 pounds.
- I will exercise more.

Action plans are derived from goals. They define the specific steps that will lead to accomplishment of the goal. An action plan includes objective measures of quantity and time and should be relatively easy to accomplish. Action plans are associated with a greater degree of success and greater self-efficacy than longer-term goals [155]. Examples of action plans are:

- I will eat a small serving of fresh fruit every day as my afternoon snack for one week.
- I will follow the plate method at lunch and dinner for one week.
- In the next week, I will walk for 25 minutes in the morning for five days.

The action plan must be realistically attainable. To determine if the plan is achievable, ask your patient to use a confidence scale to ascertain the feasibility of an action plan. It is often helpful to have a picture of a ruler, numbered 0 to 10, a Likert scale, or another depiction of a linear scale that the patient can point to or write upon. Specify that 0 should be chosen if he or she is unsure if completing the action plan is possible; 10 means he or she is very sure it can be accomplished. If the patient reports a confidence level of less than 7, it indicates that he or she has made a plan that is not realistic. In these cases, help the patient revise the action plan to one that gives a confidence level of at least 7. For example:

- Original action plan scored confidence level of 5: I will eat one small serving of fresh fruit every day as my afternoon snack for one week.
- Revised action plan scores confidence level 8: I will eat one small piece of fresh fruit five days per week as my afternoon snack for one week.

Notice that a small change in the action plan can make it more realistic.

As with all behavior change plans, the action plan and its revisions are developed in collaboration with the patient and use the strategies that he or she has chosen. The action plan should support self-efficacy. Success in achieving a positive action is more important than the quantity of a clinical measure. Success breeds confidence that one can make positive lifestyle changes.

MOTIVATIONAL INTERVIEWING

While many patients might concur that some degree of lifestyle change would be beneficial, a significant number will be ambivalent about taking concrete action. Some will be entirely resistant to change, demonstrating a lack of readiness by denying the problem or any need to make behavior change. Others may already be taking action but still need to maintain the changes over time. Motivational interviewing is a dynamic strategy for guiding patients through all of these stages of change. William R. Miller originally developed this method in 1983 to help problem drinkers and was later joined by Stephen Rollnick to formalize this revolutionary concept in promoting health behavior change in other areas [156; 157].

When patients have a condition such as prediabetes, in which lifestyle modification is the primary treatment, simply giving advice is usually not enough to instigate significant change. In fact, when working with patients to make behavior change, one should expect one's role as the authority figure to diminish while their authority increases. This is because patients usually have their own answers when it comes to lifestyle modification, although they are often unacknowledged. Patients usually know what they need to do and may even have some ideas for how they might do it, but they often resist or feel ambivalent about taking action. What they need is help in becoming aware of their own resources, feeling more confident in their ability to change, and learning to put their ideas into action. Therefore, counseling a patient on health behavior change means healthcare professionals surrender the role of expert in exchange for becoming a guide.

Motivational interviewing is a therapeutic communication strategy that facilitates behavior change by focusing on a person's current interests and concerns. It creates an atmosphere in which the patient generates his or her own reasons for change. Motivational interviewing is appropriate to use in any situation in which behavior change is indicated, including with people who are resistant to change and those who lack the confidence or motivation to make change.

Motivational interviewing recognizes that there is a natural human tendency to resist being told what to do by others and that it is difficult for people to break through well-established behavioral rituals. Failure to change health-related behaviors is often in conflict with the healthcare providers' inclination to help, heal, and prevent harm. However, people who engage in unhealthy behaviors are usually already aware of what they should be doing instead.

The process of motivational interviewing identifies people who are resistant to change and allows the provider to "roll with the resistance" rather than challenge it. This intervention capitalizes on a person's ambivalence about behavior change, exploring the discrepancy between personal goals and actual behavior. Importantly, it evokes a person's own reasons for making behavior change and his or her resources for making it happen.

Patients resist behavior change for many reasons. One reason is that it is usually easier to maintain established habits than to change them. People may also be afraid of failure, or they may have anger or a lack of confidence in their ability to change. Indicators of resistance to change may include changing the subject during a discussion, arguing, or denying the problem. When patients are clearly not ready to make behavior change, resist the urge to try to talk them into it, as this runs the risk of putting them on the defensive and making them argue in favor of staying the same. When patients repeatedly argue against change, the undesired behavior is actually reinforced. At this point, it is best to remain nonjudgmental and to keep the lines of communication open for future discussion. Examples of responses to a patient who is not willing to change are:

- It sounds like you feel the benefits of staying the same are greater than the benefits of making the change.
- What might help you be more ready to make some changes in your eating?
- Would you be interested in learning any more about resources we have for helping you eat healthier?

Many patients are ambivalent about changing. This means that they recognize the need for change and would like to do it, but they are also keenly aware of the advantages of staying the same. Ambivalence about behavior change represents both an opportunity and a hindrance. For example, the patient knows that being overweight is unhealthy but does not want to change his or her eating habits, saying, "I would like to lose weight, but I love to eat!" Notice that the patient first thinks of a reason to change, but cancels it out by thinking of the reasons not to change. These types of statements are known as "change talk." Because the patient has said he or she would like to lose weight, the perceived benefits and hypothetical solutions can be explored. The goal is to raise the patient's level of readiness to change by discovering and amplifying his or her own reasons and ways to do it. In this scenario, patients may be encouraged to talk about why they would like to lose weight and the benefits they would reap from it. For example, one could say, "Although you love to eat, you feel there would be some advantages to losing weight. What would be some of those advantages?" By having the patient state the benefits of losing weight, the patient's own change talk may be elicited. People are more influenced by what they hear themselves say than by what others tell them.

When patients are ambivalent, avoid giving them the opportunity to present arguments about why they do not want to change. A better alternative is to help patients voice their own arguments in favor of change. According to Rollnick et al., "If you are arguing for change and your patient is resisting and arguing against it, you're in the wrong role. You are taking all the good lines. It is the patient, rather than you, who should be voicing the arguments for behavior change" [156]. Change talk may be elicited from patients by asking them what they might like to change and how they might see themselves doing it.

Motivational interviewing involves a collaborative relationship that empowers patients to determine how they can make a difference in their own health. It is a skilled process that requires special training to realize its full potential. However, anyone can incorporate some of the basic tenets of motivational interviewing into their current practice by following these steps:

Ask open-ended, empowering questions. *(What would you like help with today?)*

Listen more than speak, and avoid interrupting the patient. *(Go on...)*

Summarize what the patient says. *(From what you have told me, you are worried about how prediabetes will affect your health.)*

Provide information in a neutral manner. *(Now that you know what the experts recommend for exercise, how do you think that would fit into your life? Your weight today is 178 pounds. What do you think about that?)*

Offer choices and negotiate the agenda. *(Of the things that you can do to lose weight, which one(s) would you like to work on most?)*

Listen for and respond to change talk. *(It sounds like you have been thinking about exercising more. How would exercise make your life better?)*

Evoke patients' own reasons for change. *(What benefits might you gain from getting more exercise? How important do you think this is?)*

Explore ambivalence. *(What do you like about the way things are now? What benefits would you get from exercising more?)*

Summarize what the patient is telling you. *(On one hand, I hear you saying that it would take some work on your part to exercise regularly, but on the other hand, you would feel better about yourself if you did it.)*

Assess readiness to change. *(How ready do you feel to become more physically active? On a scale of 0 to 10, how ready are you to start getting more exercise? Why did you choose that number?)*

Help your patient explore solutions. *(What has worked for you in the past? What could you see yourself doing now? What would you like about doing this?)*

Assess confidence. *(On a scale of 0 to 10, how ready are you to start exercising? Why did you choose that number? What would it take for you to have a higher number on this scale?)*

Roll with resistance and honor autonomy. *(The final decision for change is up to you. For now, it sounds like the benefits of staying the same are greater than the benefits of changing. How do you feel about keeping things the way they are?)*

Affirm the patient's statements and support self-efficacy. *(You have come up with some good ideas for how you can get more exercise. I feel confident that if you do choose to exercise, you will find a way to make it happen.)*

TOBACCO CESSATION

It is widely known that tobacco abuse is associated with a vast number of adverse health outcomes. All healthcare providers are charged with assessing patients' use of tobacco, advising them to quit, and offering strategies to help them quit. This role takes on even greater importance when working with people who have diabetes and prediabetes. Both of these conditions are independent risk factors for arterial and cardiovascular disease, and the toxic effects of smoking potentiate these risks. Tobacco use is also associated with increased incidence and severity of microvascular complications of diabetes. U.S. Public Health Service guidelines recommend that all patients be asked [158]:

- Do you smoke?
- Would you like to quit?

If a patient wants to quit, draw upon the same armament of strategies used to help motivate other health behavior change, such as losing weight, eating more healthfully, and exercising. In addition, tobacco cessation programs and pharmacologic agents are often effective. For patients who are not ready to quit, employ the same strategies discussed for people in the precontemplative stage of change.

Nicotine replacement therapy is effective in helping people stop tobacco use. This includes patches, gum, lozenges, inhalers, and nasal spray. Bupropion was the first non-nicotine pharmacotherapy for the treatment of tobacco dependence with proven efficacy [159]. Cessation rates have been reported to improve when drug therapy combines nicotine replacement with the antidepressant bupropion [160; 161]. However, in its 2020 guideline for initiating pharmacologic treatment of tobacco-dependent adults, the American Thoracic Society (ATS) recommends varenicline over both bupropion and a nicotine patch for tobacco-dependent adults. In adults who are not ready to discontinue tobacco use, the ATS recommends beginning treatment with varenicline rather than waiting until patients are ready to stop tobacco use [159].

Not surprisingly, tobacco cessation has high rates of relapse, and most people require multiple quit attempts to remain permanently tobacco-free. After 12 weeks of abstinence, about 43% of people return to regular smoking. However, longer periods of abstinence increase long-term success rates. After five years of abstinence, relapse rates drop to about 7% [153]. This presents an opportunity to help patients understand that tobacco cessation is a long-term process and previous attempts provide learning opportunities for the next attempt.

FOLLOW-UP AND REFERRAL

When health care involves behavior change, multiple encounters with a healthcare provider over an extended period of time seem to be most effective [2; 109; 155]. While the DPP was an intensive lifestyle change program, subsequent research indicates that follow-up may not need to be intensive. Rather, there is evidence to support that short, nonintensive encounters over time can be effective. Email or telephone encounters are appropriate when time and resources are limited. The important factor appears to be that the patient receives ongoing support from the healthcare team in some manner. Follow-up encounters should include checking on progress toward behavioral goals and troubleshooting challenges. Action plans may be revised or updated according to the patient's progress. While clinical measures, such as body weight, blood glucose, cholesterol, and blood pressure, must be done periodically, the focus of intervening encounters should be on behavior change and progress toward behavioral goals.

When feasible, patients with prediabetes should be referred to a registered dietitian for medical nutritional therapy [13]. Ideally, an exercise physiologist or other expert in physical fitness can recommend and support an appropriate physical activity program. In any case, healthcare professionals should be prepared to help patients identify resources within their healthcare plan or the larger community to help them achieve their goals. These may include community centers, health education classes, and health clubs. Specialized classes for people with prediabetes have become more common within health care settings as the significance of this condition has grown.

HEALTH EDUCATION FOR DIABETES PREVENTION

What should be included in diabetes prevention programs?

As preventive medicine continues to emerge in today's healthcare climate, the role of the healthcare provider as educator is changing. Traditionally, standardized teaching tools have been used to provide mostly didactic and skills-based education. Today, as behavior modification becomes a larger part of medical treatment, there is less emphasis on teaching and more on coaching and guiding. The agenda for teaching must become more patient-centered in order to effectively facilitate behavior change. The patient's role is active, rather than passive. As discussed in relation to concepts of self-efficacy and motivational interviewing, patient encounters should become more collaborative and driven by the patient's agenda.

The ADCES recommends a personalized education plan for every patient with prediabetes that incorporates the same self-management principles as diabetes education. In addition to patients with established prediabetes, this education should be available to family members of people with diabetes and patients with other risk factors, such as hypertension, obesity, and dyslipidemia. The ADCES Position Statement on diabetes prevention education states that the educational program should [39]:

- Promote a basic understanding of the risk factors for developing type 2 diabetes.
- Communicate the importance of risk reduction for modifiable risk factors.
- Provide goals for dietary change and physical activity to achieve modest weight loss, taking into account the individual's unique situation.
- Emphasize that healthy eating and physical activity are ongoing lifestyle behaviors for effective weight loss and maintenance.
- Coach patients through the behavior change process.
- Instruct in self-management skills such as monitoring food intake and assessing percentage of daily fat intake.
- Recommend getting 150 minutes of moderate-intensity physical activity to per week.
- Provide follow-up to assess weight and help solve problems related to lifestyle management.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Diabetes Association, certified technology-assisted diabetes prevention programs may be effective in preventing type 2 diabetes and should be considered.

(https://diabetesjournals.org/care/issue/47/Supplement_1. Last accessed January 10, 2024.)

Level of Evidence: B (Supportive evidence from well-conducted cohort and/or case-control studies)

Topics included in diabetes prevention programs include [72; 162]:

- Definition of prediabetes
- Health risks associated with prediabetes
- Identifying modifiable risk factors
- Lifestyle interventions to prevent progression to type 2 diabetes
- Significance of cardiovascular health and risk reduction
- Healthy eating behaviors
- Exercise recommendation
- Weight-loss strategies
- Assessing readiness to change
- Overcoming barriers to lifestyle change
- Goal setting and action planning
- Medical follow up to monitor blood glucose, lipids, weight, and blood pressure
- Signs and symptoms of hyperglycemia and when to call a healthcare provider

PREDIABETES EDUCATION PROGRAMS

Education to prevent diabetes is taking place on a national level. Under the new healthcare reform legislation, the CDC has authorized the establishment of a National Diabetes Prevention Program [163]. The DPP and follow-up studies have clearly demonstrated that lifestyle modification is the critical element in preventing progression from prediabetes to type 2 diabetes. CDC-recognized lifestyle change programs are a key component of the DPP [164]. Multiple studies suggest that intensive interventions, taking place over multiple sessions, are most effective [2; 109; 165]. Clinical experts, such as registered dietitians and nurses, as well as trained peers and laypersons appear to be efficacious in delivering this education [165; 166]. The Healthy Living Partnerships to Prevent Diabetes (HELP PD) study was a community-based lifestyle intervention program modeled after the DPP. The program design included [165]:

- Lifestyle interventions provided by registered dietitians and lay community health workers
- Initial six-month intensive phase with weekly group meetings using DVDs developed from the DPP curriculum
- Maintenance intervention beginning at six months, including weekly group meetings and additional phone or personal contact with community health workers

In this study, the control group received care consisting of two visits with a registered dietitian and a quarterly newsletter with tips for lifestyle changes. Results included a decrease in blood glucose levels of more than 4 mg/dL in the study group, compared to 0.3 mg/dL reduction in the control group [165]. The intensively treated group also achieved a weight loss of 7.3% and a 5.9 cm decrease in waist circumference after one year. The control group lost only 1.3% of body weight and had a decrease in waist circumference of only 0.8 cm.

One study examined the impact of DPP intervention on blood glucose and adiposity beyond 12 months of follow-up. This randomized controlled trial compared a 24-month lifestyle weight-loss program to an enhanced usual care condition in participants with prediabetes. The lifestyle weight-loss program sought to induce 7% weight loss at six months that would be maintained over time through decreased caloric intake and increased physical activity. The usual care group received two visits with a registered dietitian and a monthly newsletter. Results revealed that the lifestyle weight-loss program participants experienced greater decreases in fasting glucose (-4.35 mg/dL); body weight (-4.19 kg); and waist circumference (-3.23 cm) [167].

In another pilot study, people with prediabetes in rural Montana participated in a prevention program implementing the DPP lifestyle interventions through a 16-week telehealth program [166]. In this program, education was delivered by video teleconferencing to participants. Coaches and participants at both sites could see and hear each other through videoconferencing equipment. The program consisted of 16 weekly core curriculum sessions followed by six monthly after-core sessions [166]. Results of this pilot study demonstrated that a telehealth program could be just as effective as face-to-face participation. Participants in both groups had similar results, including increasing their physical activity levels and achieving a 7% weight loss. Other alternatives to intensive one-to-one counseling could include follow-up by telephone, email, or Internet-based interactive programs.

COST EFFECTIVENESS OF DIABETES PREVENTION PROGRAMS

The criterion standard for preventing diabetes in high-risk populations is intensive lifestyle intervention over an extended period. However, this type of program is labor- and resource-intensive and requires dedicated staff. Limited resources can influence the feasibility of funding and developing new programs.

Analysis of the DPP has shown that the interventions to prevent progression to type 2 diabetes in high-risk people can be cost effective from both societal and health systems perspectives. While the design of the DPP comprised intensive individual coaching and follow-up, group education sessions will increase its cost effectiveness. For diabetes self-management, group education is known to be as effective as individual education, and this is most likely true for prediabetes education as well [39].

Most studies on the effectiveness of diabetes prevention programs have examined intensive, multisession programs. More research is needed to explore the efficacy and cost effectiveness of diabetes prevention programs that use alternate formats. There has been limited research on the effectiveness of single-session classes. One study, however, demonstrated that a single session of motivational interviewing by telephone had a positive effect on lipid profiles and physical activity level [168]. A systematic review and meta-analysis found that the use of mobile text messaging for conveying type 2 diabetes interventions was effective for glycemic control [169]. Additionally, a feasibility study found that sending short text messages in conjunction with conventional diabetes treatment improved glycemic control and positively influenced other aspects of diabetes self-care in individuals with type 2 diabetes [170].

Time limitations in healthcare practice are generally ubiquitous, and all of the interventions for diabetes prevention may require more than a single 15-minute or brief messaging interaction. Efficiency can be maximized by using resources wisely. Consider how the rest of the healthcare team can assist the patient, and be familiar with other resources within the healthcare setting. Consider a referral to a dietitian or other healthy lifestyle resource, such as weight management, healthy eating, and exercise classes. Become familiar with community-based resources for diabetes prevention, weight loss, exercise, and general health promotion. Utilize the numerous online resources; many of them are interactive, which can enhance the patient's experience. Refer to the ***Resources*** section of this course for additional information.

HEALTH LITERACY

Interest in and understanding of health literacy has grown tremendously over the last 20 years. It has been an important component of the Healthy People initiative as well as Title V of The Patient Protection and Affordable Care Act of 2010, which defines health literacy as the degree to which a person can obtain, communicate, process, and understand basic health information and services to make appropriate health decisions [171]. Healthy People 2030 contains an updated definition that includes personal health literacy as well as organizational health literacy. The new definitions emphasize the ability to use health information rather than to just understand it; focus on the ability to make "well-informed" decisions as opposed to "appropriate" ones; incorporate a public health perspective; and acknowledge that organizations have a responsibility to address health literacy [171].

The government reports that nearly 90% of Americans have difficulty utilizing the health information that is routinely provided in healthcare facilities and in the media [172]. This is unsurprising when one considers that most Americans have never had a course in anatomy or physiology and that the average high school graduate has had a total of one health sciences class. Also notable is that only 12% of English-speaking adults in the United States have proficient health literacy skills [172].

Low health literacy has been associated with increased usage of the healthcare system. United Health Group reports that improving health literacy could prevent nearly one million hospital visits and save more than $25 billion each year [173]. Effects of low health literacy include improper medication use, nonadherence to prescribed regimens, inability to make appropriate healthcare decisions, and ineffective self-care behaviors [174]. In people with diabetes, low health literacy has been associated with poor glycemic control, an increase in diabetic retinopathy, and hypoglycemia [175; 176]. A study conducted by the U.S. Department of Education found that adults who self-report the worst health also have the most limited literacy, numeracy, and health literacy skills [177].

Numeracy is a part of literacy that includes concepts having to do with numbers and basic mathematical functions. It includes "the ability to access, use, interpret, and communicate mathematical information and ideas, to engage in and manage mathematical demands of a range of situations in adult life" [178]. Numeracy is important for patients with diabetes and prediabetes, in which there is a need to read food labels, calculate nutrient value percentages, and interpret blood glucose values, among other skills.

Following research completed since 1990, the USDHHS has formulated the National Action Plan to Improve Health Literacy, an initiative to restructure the ways health information is created and disseminated in the United States. It calls upon multiple sectors, such as policymakers, organizations, communities, and individuals, to improve health literacy [172]. The National Action Plan is based upon the premise that improved health literacy supports patient-centered care. Patients who have access to understandable health information are more empowered to take appropriate action with their health.

There are many ways that healthcare professionals can easily incorporate improved health literacy into professional practice. First, make it a point to use plain language, both verbally and in writing, when interacting with patients. Avoid medical terms and jargon as much as possible. For example, "high blood sugar" is simpler than "elevated blood glucose" and "heart disease" or "heart problems" are simpler than "cardiovascular complications." The CDC's Health Literacy website contains information about guidelines, laws, and standards for health literacy and plain language that can help healthcare professionals create and use health information that is accurate, accessible, and actionable [179].

Visual aids can improve patients' understanding as well. Food models and pictures can be used, including the plate method. Understand that most adults need to hear something more than once before being able to commit it to knowledge. Therefore, use repetition and vary the way the same concept is explained. Many times, the amount of information healthcare professionals are expected to disseminate can be overwhelming. If healthcare professionals are overwhelmed by the information, it is safe to assume patients will be as well. Patients recall only about one-half of the health information provided to them [180]. Therefore, provide related information in "chunks" and limit new information to one to three "need to know" concepts at one time. This provides an excellent opportunity to apply skills in providing patient-centered care, asking patients what they would like to work on most. Continue to check for understanding and encourage questions.

The teach-back method is recommended for improved health literacy [180]. This is a way to clarify patients' understanding of what has been taught. Teach back consists of asking patients to recount, in their own words, what they heard. This will allow for assessment of misunderstandings and gaps in learning. When using teach back, avoid making the patient feel threatened by framing the request in a way that centers any inadequacies on the healthcare system or provider. For example, one could say, "I would like to make sure I explained the plate method well to you. Can you tell me, in your own words, how you would use it to help you decide what to eat?"

Verbal instructions should be supplemented with written material. However, written material should be designed for the majority and follow appropriate guidelines for health literacy. Health information translated to other languages from English should maintain the health literacy standards of the original piece. Health education literature should also look easy to read, having a font size of 12 to 14 points. Written materials should have plenty of white space on the paper. About 25% to 35% of the page should be white, and margins should be no smaller than one-half inch. Graphics can help enhance literacy if they are appropriate in content and size and to the meaning to the document.

CULTURAL CONSIDERATIONS IN PREDIABETES EDUCATION

Culturally appropriate programs have proven effective for diabetes education and similar programs should likewise be appropriate for prediabetes education. Project Dulce is a community-based diabetes education program in San Diego, California, that uses bilingual peer educators, known as *promotoras*, to educate and support members of their own cultural or ethnic group [181]. The *promotoras* are trained lay members of a nurse-led healthcare team that adheres to clinical standards of diabetes disease management. The Project Dulce team collaborates with the participants' own healthcare providers in ensuring that care and education follows established protocols. Originally developed for the Hispanic/Latino population, Project Dulce has now been adapted for the African American, Filipino, and Vietnamese populations.

Other culturally relevant programs are currently being tested in different parts of the United States [182]. The Health Native Community Partnership is an organization devoted to empowering Native Americans to take action to promote the wellness of themselves and their community. Native Lifestyle Balance is a diabetes prevention program based on the DPP with cultural adaptations for this group [183].

CASE STUDY

Patient S is a White woman who is 48 years of age. At a recent routine physical examination, she learns that her fasting blood glucose is 118 mg/dL. With a height of 5 feet 5 inches and a weight of 162 pounds, her BMI is 28, placing her in the category of overweight. Her physician refers her to Nurse A, a diabetes educator, for counseling and education on the prevention of diabetes, instructing her to keep a food diary and bring it to the appointment.

Nurse A begins the encounter by taking steps to develop a collaborative relationship with Patient S, first performing a learning needs assessment by asking her what she already knows about prediabetes and its risks and treatment. Nurse A determines what she wants to learn and what her goals are. Next, the patients' social situation and support system are assessed, including how family, work, and other obligations affect her lifestyle choices. Nurse A inquires regarding past smoking or alcohol use. Finally, the nurse asks what, if anything, the patient has started doing, or would like to start doing, to help herself prevent diabetes.

Patient S's physician had given her basic information on prediabetes and advised her to lose weight and begin exercising. The patient read the booklet on prediabetes and seems to have a reasonable understanding of her condition and the recommendations for treating it. However, she says she feels overwhelmed with the thought of making major lifestyle changes. She says, "I know I need to make changes, but I just can't get myself to do it." To decrease her anxiety and build self-efficacy, Nurse A replies, "The thought of change can be scary, but if you really want to, I am confident we can find some ways to help you do it."

This is a good time to assess the patient's readiness to change. Although she has some reluctance, Patient S rates her readiness to change as 8 on a scale from 0 to 10. She states that she will be going on vacation next week but will feel ready to make changes when she returns.

The next step is to negotiate an agenda for the encounter. Given that Patient S understands the basic treatment recommendations for prediabetes, the nurse asks what she would like to begin working on first. She says that she knows she needs to lose weight and wishes she could. With her permission, Nurse A takes the opportunity to educate her on the research that shows she can prevent or delay diabetes onset by losing 5% to 7% of her current body weight, which is 8 to 11 pounds. To help Patient S make realistic weight loss goals, the nurse asks, "Would you say that losing 8 pounds is something you could work on?" The patient is surprised that she only needs to lose 8 pounds; she had expected more than that. Nurse A supports the idea of greater weight loss eventually but suggests starting with 8 pounds and working from there. The nurse explains that her success in losing a few pounds at first increases the likelihood that she can lose more later.

While Patient S agrees that an 8-pound weight loss is reasonable, she remains ambivalent about making the necessary lifestyle changes. She says, "I really hope I can do this, but I'll probably never maintain it." The nurse recognizes this as change talk and takes the opportunity to explore it by asking, "Can you name three benefits you would enjoy if you did lose 8 pounds?" Patient S replies that she would drop a dress size, she would feel good about preventing diabetes, and it would motivate her to continue losing more weight.

Now that the patient has a realistic goal to lose 8 pounds, it is time to make an action plan that specifies the steps she will take to meet her goal. Nurse A starts by reviewing the key tenets of weight loss: eating less, lowering fat and calories in her diet, increasing fiber intake, and/or increasing exercise. The nurse demonstrates the plate method to the patient as a simple model for healthy eating and asks, "Which of these would you like to start working on today?" Patient S replies that she would like to do all of them, but says she is afraid it will take too much time to do all of these things. Once again, this is recognized as change talk, and Nurse A replies, "So is it safe to say that you think making some changes is worth a try?" With her consent, Nurse A begins helping Patient S specify her action plan by asking to review her food diary with her. Together, the nurse and patient determine that:

- She eats a moderate amount of fruits, vegetables, and whole grain.
- She eats high-fat, sweet, dessert-type foods once or twice every day.
- She usually chooses refined-grain products.
- She uses fattening toppings and spreads on salads, vegetables, and sandwiches.
- She often eats large portion sizes.
- She eats cereal and fat-free milk for breakfast every day.
- Her primary source of protein is chicken, prepared in a variety of ways.

Patient S's food diary reveals areas in which she can capitalize on healthy choices she is already making. Nurse A points out that she eats fruits, vegetables, and whole grains, eats breakfast, uses fat-free milk, and does not eat large amounts of saturated animal fat. Collaboratively, the two formulate a list of possible dietary changes based on her diary. Of these things, Nurse A asks her to pick two or three that she would like to start working on right away. She makes the following choices:

- Decrease intake of refined carbohydrates while increasing intake of whole grains.
- Reduce portion sizes.
- Reduce use of fattening toppings on salads, vegetables, and sandwiches.

Next, Patient S writes action plans for each of her behavior change choices. Nurse A assists the patient to begin formulating an action plan for her first choice by asking the following questions:

- *What will you do?* I will reduce my intake of refined carbohydrates while increasing my intake of whole grains.

- *How will you do it?* I will substitute whole-grain cereal and crackers for refined carbohydrate snacks and sweets.
- *How much?* I will eat one-half cup whole-grain cereal or six whole-grain crackers in place of my usual refined carbohydrate snack.
- *How often?* I will do this every day.

Patient S's completed action plan is to eat one-half cup whole-grain cereal or six whole-grain crackers every day in place of refined carbohydrate snacks.

The next step in making an action plan is to measure the patient's confidence in her ability to carry out the plan and to help her make modifications if needed. Patient S is asked to circle a number on a scale of 0 to 10 rating her confidence. She circles the number 6.

A confidence rating of 7 or more indicates that a person is reasonably confident in his or her ability to carry out the action plan. Because Patient S rated her confidence level as 6, it indicates that this action plan is probably not achievable for her. Nurse A asks her what would be more realistic, and she replies, "If I could just have a sweet treat on the weekend!" The nurse prompts her to change the "how often" part of her action plan from "every day" to "five days per week." With this modification, Patient S rates her confidence in the action plan as 9. Obviously, refraining entirely from sweet treats is desirable, but if she does not have the self-efficacy to do this, Patient S's action plan has a high risk for failure. It is better for her to experience success with small steps and build from there with future action plans.

If time allows, the nurse may continue helping the patient formulate action plans for her other chosen behavior changes. Her readiness to set a goal and make an action plan for exercise should be assessed using the same methods. With many people, especially if they are overwhelmed or lack self-efficacy, it is best to be conservative in the number of action plans they make initially. Too many action plans may be unrealistic. Usually, two or three action plans at a time is reasonable. Remind patients that when they achieve one action plan, they can begin to add more and build on their success over time.

Although there is not time for Nurse A to help Patient S formulate action plans for all of her chosen behavior changes, she has empowered her to make her own action plans. Nurse A asks the patient to report her subsequent action plans by phone, email, or at a future visit.

CONCLUSION

The rising costs of health care and increasing incidence of chronic conditions related to the modern lifestyle have changed our approach to medicine. Diabetes is particularly significant because it affects millions of people and is associated with an unprecedented financial burden and incalculable toll on individuals and society. In 2002, the results of the DDP represented a major breakthrough in appreciation for the benefits of lifestyle modification on health promotion and disease prevention. Since that time, numerous studies have supported the findings of the DPP, and many disease-prevention projects based on the DPP have been implemented throughout the nation and the world.

A multitude of authoritative bodies have developed lifestyle recommendations based on the findings of the DPP. These recommendations include eating a balanced diet abundant in plant-based foods, reducing fat and calories, and practicing moderation with salt and alcohol consumption. Several strategies for helping patients lose weight and maintain weight loss have been presented in this course. The benefits of exercise to health are well known, but the DPP showed a specific benefit with regard to the prevention of diabetes.

This course has also examined the importance of diabetes prevention in diverse populations, such as children, people of different cultural groups, and those with variations in health literacy. Healthcare providers working with diverse cultural groups require an adequate degree of cultural competency in order to understand and respond to variances in food and exercise preferences among different populations.

Helping a patient with prediabetes prevent progression to type 2 diabetes involves more than clinical knowledge and the transfer of that information.

Developing a collaborative relationship is key to helping patients with behavior change. Motivational interviewing is a valuable skill whereby the provider helps patients explore ambivalence about making change and set their own agendas when they are ready to make changes. Studies have shown that intensive and regular intervention over time are most effective for achieving and maintaining health behavior change.

RESOURCES

Many resources and printable tools are available online to help healthcare professionals in assisting patients with lifestyle change, behavior modification, and diabetes prevention.

INTERACTIVE FOOD AND ACTIVITY TRACKERS

MyPlate

Allows patients to compare food intake patterns with suggested portion sizes using a plate as a template. Includes an interactive food tracker and planner.
https://www.myplate.gov

PRINTABLE FOOD AND ACTIVITY DIARIES

Centers for Disease Control and Prevention
My Food and Beverage Diary
https://www.cdc.gov/healthyweight/pdf/food_diary_cdc.pdf

Centers for Disease Control and Prevention
My Physical Activity Diary
https://www.cdc.gov/healthyweight/pdf/Physical_Activity_Diary_CDC.pdf

National Heart, Lung, and Blood Institute
Daily Food and Activity Diary
https://www.nhlbi.nih.gov/health/educational/lose_wt/eat/diaryint.htm

Harvard Health Food Diary
https://www.health.harvard.edu/media/content/files/health-report-pdfs/Food-Diary.pdf

TOOLS FOR THE DEVELOPMENT OF DIABETES PREVENTION PROGRAMS

Diabetes Prevention Program
Lifestyle Manuals of Operations
Provides curriculum materials from the Diabetes Prevention Program.
https://dppos.bsc.gwu.edu/web/dppos/lifestyle

Native Lifestyle Balance
A diabetes prevention program based on the DPP with cultural adaptations for Native Americans.
https://hncpartners.org

Association of Diabetes Care and Education Specialists
ADCES7 Self-Care Behaviors
An Internet-based suite of tools for diabetes education available for purchase.
https://www.adces.org/diabetes-education-dsmes/adces7-self-care-behaviors

TEACHING TOOLS

Centers for Disease Control
and Prevention: Physical Activity
Provides tips on becoming active and videos demonstrating proper form for muscle-strengthening activities.
https://www.cdc.gov/physicalactivity

Your Guide to Lowering Your Blood Pressure with DASH
https://www.nhlbi.nih.gov/files/docs/public/heart/new_dash.pdf

Association of Diabetes Care and Education Specialists
Tools and Resources
Free downloadable patient education handouts, a guidebook, and short video on the seven key behaviors for diabetes management.
https://www.adces.org/diabetes-education-dsmes/adces7-self-care-behaviors

National Heart, Lung, and
Blood Institute Serving Size Card
A wallet-sized guide to estimating portion sizes as compared to common everyday objects.
https://www.nhlbi.nih.gov/health/educational/wecan/downloads/servingcard7.pdf

DIVERSITY AND HEALTH LITERACY

National Institute of Diabetes
and Digestive and Kidney Diseases
Staying Active at Any Size
Health and weight management information.
https://www.niddk.nih.gov/health-information/weight-management/staying-active-at-any-size

Oldways
Cultural Food Traditions
Mediterranean, African heritage, Latin American, Asian, and vegetarian and vegan food pyramids.
https://oldwayspt.org

Centers for Disease Control
and Prevention: Health Literacy
A site for health communicators, public health professionals, and community leaders who seek information and tools on health literacy research, practice, and evaluation.
https://www.cdc.gov/healthliteracy

GLOSSARY OF TERMS

Acanthosis nigricans: Inflammatory skin condition causing dark, velvety papillary growth and discoloration in skin folds and neckline, associated with insulin resistance.

Bariatrics: Branch of medicine dealing with prevention and treatment of obesity.

C-reactive protein: A protein found in the blood, levels of which rise in response to inflammation. Associated with unstable coronary artery disease.

Exogenous: Originating outside the body or an organ. For example, injected insulin is an exogenous source of insulin.

Fibrinogen: Protein in blood plasma essential for blood clotting.

Hydrogenation: A chemical process that converts liquid fats to solid fats. Partial hydrogenation of liquid oils produces trans fatty acids. Trans fatty acids can be found in margarine, shortening, and many commercial baked foods.

Hyperinsulinemia: Excessive amount of insulin in the blood.

Gluconeogenesis: The formation of glucose in the liver from stored fats and proteins.

HDL cholesterol: The "good" cholesterol consisting of high-density lipoproteins. A high level in the blood is thought to lower the risk of coronary artery disease.

Hirsutism: Condition characterized by the excessive growth of hair or presence of hair in unusual places.

Hyperandrogenism: An excessive production of male hormones.

Incretins: A group of gastrointestinal hormones that cause an increase in the amount of insulin released from the beta cells of the islets of Langerhans after eating, even before blood glucose levels become elevated.

Microalbuminuria: Small amounts of protein found in the urine. A highly sensitive indicator of glomerular disease and a sign that kidneys are not functioning properly.

Microvascular complications: Damage to small blood vessels over time; usually caused by prolonged hyperglycemia. It is responsible for the eye, kidney, and nerve damage associated with uncontrolled diabetes.

Polydipsia: Excessive thirst, often symptomatic of elevated blood glucose.

Polyunsaturated fatty acids: An unsaturated fatty acid whose carbon chain has more than one double or triple valence bond per molecule; found chiefly in fish, corn, soybean oil, safflower oil, and walnuts. Can reduce the cholesterol levels in blood and lower risk of heart disease when used in moderate amounts.

Polyuria: Excessive urination, often symptomatic of elevated blood glucose.

Sarcopenia: Age-related loss of skeletal muscle resulting in frailty.

Saturated fat: Fats that contain the maximum amount of hydrogen possible, such as those found in meats and dairy products; can contribute to coronary heart disease and the development of some cancers.

Trans fatty acid: A fat that is produced when liquid fat (oil) is turned into solid fat through a chemical process called hydrogenation. Eating a large amount of trans fatty acids also raises blood cholesterol and risk of heart disease.

Triglycerides: A common blood fat that triggers the liver to create more cholesterol. High levels of triglycerides are usually indicative of high levels of insulin. The ratio of triglycerides to HDL is a powerful indicator of insulin levels and is strongly predictive of future cardiovascular events.

Customer Information/Evaluation insert located between pages 48–49.

Course Availability List

These courses may be ordered by mail on the Customer Information form located between pages 48–49.
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BREAST CANCER

#30613 • 15 ANCC / 6 Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to provide nurses and allied health professionals with the information necessary to accurately diagnose and effectively treat patients with breast cancer according to established guidelines, with the ultimate goal of improving patient care and quality of life.
Faculty: Jacqueline Houtman, RN, MA, CDP
Audience: This course is designed for nurses and allied healthcare professionals invested in the care, delivery of treatment, and relevant education of patients with breast cancer.
Additional Approval: AACN Synergy CERP Category A, CCMC

MULTIPLE MYELOMA

#30714 • 10 ANCC / 4 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: Multiple myeloma is the second most prevalent hematologic cancer after non-Hodgkin lymphoma. While great strides have been made to improve survival rates with this disease, and positive outcomes have been attained over the last ten years, multiple myeloma remains an incurable disease. The purpose of this course is to provide healthcare professionals in contact with multiple myeloma patients the information necessary to provide optimum care, treatment, and patient education.
Faculty: Jacqueline Houtman, RN, MA, CDP
Audience: This course is designed for nurses and allied healthcare professionals involved in the care, treatment, and education of patients with the diagnosis of multiple myeloma.
Additional Approval: AACN Synergy CERP Category A, CCMC

HYPEREMESIS GRAVIDARUM

UPDATE

#33174 • 5 ANCC / 1 Pharm Hour

Book By Mail – $38 • ONLINE – $30

Purpose: Practitioners commonly treat nausea and vomiting in early pregnancy, regardless of whether the patient fits all the criteria of a diagnosis of hyperemesis gravidarum. The purpose of this course is to increase the awareness of hyperemesis gravidarum and present guidelines for nursing management of the condition.
Faculty: Sandra Mesics, CNM, MSN, RN
Audience: This course is designed for all nurses, especially those working in obstetrics and maternal/child nursing.
Additional Approval: AACN Synergy CERP Category A, CCMC

CLINICAL USE OF NEUROMUSCULAR BLOCKING AGENTS

UPDATE

#35111 • 10 ANCC / 10 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide intensive care, emergency, and prehospital providers with the clinical knowledge to administer neuromuscular blocking agents in a safe and effective fashion, as well as to know how such agents can be effectively monitored and, ultimately, safely and efficiently reversed.
Faculty: Richard E. Haas, RN, MSN, EdM, PhD, CRNA, PHRN, LTC (Retired)
Audience: This course is designed for nurses, nurse practitioners, and other allied health professionals in a variety of settings, including the intensive care unit, emergency department, acute care, prehospital settings, critical care, and post-anesthesia care.
Additional Approval: AACN Synergy CERP Category A

MODERATE SEDATION

#40953 • 5 ANCC Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of the course is to provide physicians with the information necessary to perform moderate sedation safely and according to existing guidelines in order to facilitate better patient care.
Faculty: Lori L. Alexander, MTPW, ELS, MWC
Audience: This course is designed for physicians in a variety of settings, including private practice, emergency department, radiology department, cardiac catheterization lab, and ambulatory surgery centers. The course is also of benefit to private practice physicians in family medicine and virtually all specialty areas.

DIAGNOSIS AND MANAGEMENT OF CHRONIC KIDNEY DISEASE IN PRIMARY CARE

#48763 • 5 ANCC Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide physicians and physician assistants with the information necessary to develop treatment regimens associated with optimal adherence and provide adequate patient education, counseling, and support to patients with chronic kidney disease.
Faculty: John J. Whyte, MD, MPH; Usker Naqvi, MD
Audience: This course is designed for all primary care physicians and physician assistants involved in the care of patients with kidney disease.

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Course Availability List *(Cont'd)*

ISCHEMIC STROKE
#90284 • 10 ANCC / 5 Pharm Hours
Book By Mail – $68 • ONLINE – $60
UPDATE

Purpose: The early identification and management of the risk factors for ischemic stroke can lead to substantial health benefits and reductions in cost. However, research has documented gaps between healthcare professionals' knowledge and practice with respect to prevention, demonstrating that adherence to evidence-based or guideline-endorsed recommendations pertaining to all interventions for primary and secondary prevention are underutilized or ineffective. The purpose of this course is to provide needed information about the roles of diagnosis and screening, timely evaluation of individuals with suspected stroke, immediate treatment of stroke, and the elements of effective rehabilitation programs so that healthcare professionals may implement the necessary interventions appropriately.
Faculty: Lori L. Alexander, MTPW, ELS, MWC
Audience: This course is designed for physicians, nurses, and physician assistants in the primary care setting. Neurologists and other healthcare practitioners will also benefit from this course.
Additional Approval: AACN Synergy CERP Category A, CCMC

CLINICAL MANAGEMENT OF VENTRICULAR ARRHYTHMIAS
#90374 • 15 ANCC / 5 Pharm Hours
Book By Mail – $98 • ONLINE – $90
UPDATE

Purpose: The purpose of this course is to provide physicians, nurses, and other healthcare professionals with up-to-date knowledge of risk factors for development of ventricular arrhythmias, recommended therapies for the immediate and long-term management of arrhythmias, and indications of complications or side effects of therapy necessary to facilitate effective patient management, early identification of problems, and appropriate patient and family education.
Faculty: Karen Majorowicz, RN, ARNP
Audience: This course is designed for physicians, physician assistants, nurse practitioners, and nurses seeking to enhance their knowledge of ventricular arrhythmias. The course is of particular importance for clinicians in the primary care and emergency settings.
Additional Approval: AACN Synergy CERP Category A, CCMC

SAFE CLINICAL USE OF FLUOROSCOPY
#90471 • 10 ANCC Hours
Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide healthcare providers with an understanding of the challenges encountered when using fluoroscopy in clinical practice and the tenets of safe fluoroscopy use in clinical practice.
Faculty: Berthina Coleman, RN, MD
Audience: This course is designed for physicians, nurses, radiology technicians, surgical technicians, and all healthcare staff involved in ensuring safe clinical use of fluoroscopy.
Additional Approval: AACN Synergy CERP Category A

ANTIBRADYCARDIA PACEMAKERS
#90804 • 15 ANCC Hours
Book By Mail – $98 • ONLINE – $90
UPDATE

Purpose: The purpose of this course is to provide basic information on pacemaker therapy, indications for implantation, preprocedure and postprocedure care, identification and management of pacemaker malfunctions, and patient education.
Faculty: Karen Majorowicz, RN, ARNP
Audience: This course is designed for physicians, nurse practitioners, and nurses practicing in acute or adult healthcare settings.
Additional Approval: AACN Synergy CERP Category A, CCMC

CLINICAL MANAGEMENT OF ATRIAL FIBRILLATION
#90824 • 10 ANCC / 6 Pharm Hours
Book By Mail – $68 • ONLINE – $60
UPDATE

Purpose: The purpose of this course is to provide a basic review of current treatment options for the management of atrial fibrillation and indications for use, risks, and criteria for evaluating the treatment's efficacy.
Faculty: Karen Majorowicz, RN
Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals working in an adult healthcare setting, where they are likely to encounter patients who are (or should be) receiving medical intervention for control of atrial fibrillation.
Additional Approval: AACN Synergy CERP Category A, CCMC

HYPERLIPIDEMIAS AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE
#90844 • 10 ANCC / 7 Pharm Hours
Book By Mail – $68 • ONLINE – $60
UPDATE

Purpose: The purpose of this course is to provide a review of hyperlipidemia in the pathogenesis of cardiovascular disease, as well as the therapeutic benefits of pharmacologic and nonpharmacologic approaches to treatment. The objectives are to promote team-based care, foster patient awareness and shared provider-patient decision-making, and promote implementation of lifestyle changes and compliance with guideline-directed therapy for prevention of cardiovascular disease.
Faculty: A. José Lança, MD, PhD
Audience: This course is designed for physicians, physician assistants, nurses, and pharmacy professionals who may intervene to limit the effects of hyperlipidemias in their patients, promoting better long-term health and preventing cardiovascular disease.
Additional Approval: AACN Synergy CERP Category A, CCMC

MATERNAL HEALTH DISPARITIES
#93010 • 4 ANCC Hours
Book By Mail – $32 • ONLINE – $24
NEW!

Purpose: The purpose of this course is to provide healthcare providers with the knowledge and skills necessary to improve maternal outcomes in all races, ethnicities, and marginalized groups.
Faculty: Mary Franks, MSN, APRN, FNP-C
Audience: This course is designed for all healthcare providers who may intervene to improve peripartum and postpartum health care and reduce health disparities.
Additional Approval: AACN Synergy CERP Category B

Prices are subject to change.
Visit www.NetCE.com for a list of current prices.

Course Availability List *(Cont'd)*

MANAGEMENT OF OPIOID DEPENDENCY DURING PREGNANCY

#93093 • 2 ANCC / 2 Pharm Hours

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to provide healthcare professionals with the information necessary to appropriately care for pregnant women with opioid use disorder who are or are planning to become pregnant in order to minimize the adverse effects on the mother and fetus.
Faculty: Davina Moss-King, PhD, CRC, CASAC, NCC
Audience: This course is designed for substance abuse counselors, social workers, pharmacists, nurses, and any professional that assists women who are pregnant and misuse opioids. The material will also be useful for pediatric nurses working in the neonatal intensive care unit (NICU) and primary care providers in women's health care.
Additional Approval: AACN Synergy CERP Category A, CCMC

PHARMACOLOGIC AND MEDICAL ADVANCES IN OBESITY MANAGEMENT

#94280 • 15 ANCC / 12 Pharm Hours

Book By Mail – $98 • ONLINE – $90

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

SUBSTANCE USE DISORDERS AND PAIN MANAGEMENT: MATE ACT TRAINING

#95300 • 8 ANCC / 8 Pharm Hours

Book By Mail – $56 • ONLINE – $48

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute controlled substances with an appreciation for the complexities of managing patients with substance use disorders and comorbid pain in order to provide the best possible patient care and to prevent a growing social problem.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for all healthcare professionals who may alter prescribing practices or intervene to help meet the needs of patients with substance use disorders.
Additional Approval: AACN Synergy CERP Category A
Special Approval: This course meets the Federal MATE Act requirement for 8 hours of training for APRNs with a new or renewing DEA license. This course meets the requirements for opioid/controlled substance, pain management, and addiction education.

SENSORY INTEGRATION AND PROCESSING PROBLEMS: IMPACT ON CARE

#96673 • 2 ANCC Hours

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to improve the quality of care administered to patients with sensory processing issues by providing health and mental health professionals with information about sensory processing issues and health care from the point of view of the patient.
Faculty: Polly Warring, MSPT
Audience: This course is designed for clinicians involved in the care of patients with sensory processing dysfunction.
Additional Approval: AACN Synergy CERP Category A, CCMC

INTERCULTURAL COMPETENCE AND PATIENT-CENTERED CARE

#97510 • 4 ANCC Hours

Book By Mail – $32 • ONLINE – $24

Purpose: The purpose of this course is to provide members of the interprofessional healthcare team with the knowledge, skills, and strategies necessary to provide culturally competent and responsive care to all patients.
Faculty: Alice Yick Flanagan, PhD, MSW
Audience: This course is designed for all members of the interprofessional healthcare team.
Additional Approval: AACN Synergy CERP Category B

BACTERIAL SEXUALLY TRANSMITTED INFECTIONS

#98721 • 5 ANCC / 4 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to enhance clinician knowledge regarding the most common bacterial sexually transmitted infections in order to ensure that diagnosis and treatment is initiated early, when transmission risk and sequelae can be minimized.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for physicians, physician assistants, nurses, pharmacists, and allied health professionals involved in the care of patients at risk for or with bacterial sexually transmitted infections.
Additional Approval: AACN Synergy CERP Category A

IRRITABLE BOWEL SYNDROME

#98932 • 10 ANCC / 5 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide primary care physicians and nurses a review of irritable bowel syndrome, emphasizing pathophysiology, clinical assessment, and principles of care that take into account the biopsychosocial features of this common disorder. The goal is to improve clinical recognition and treatment and to promote management strategies that lead to better patient outcomes.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare providers who may improve the identification and care of patients with irritable bowel syndrome.
Additional Approval: AACN Synergy CERP Category A, CCMC

Prices are subject to change.
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	94194	Prediabetes: An Opportunity to Prevent Diabetes / 15 Contact Hours	$90

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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?

#90180
Agitation, Sedation, and Delirium in Adult ICU Patients
5 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#98394
Herbal Medications: An Evidence-Based Review
10 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#94194
Prediabetes: An Opportunity to Prevent Diabetes
15 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#90180 Agitation, Sedation, and Delirium in Adult ICU Patients — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team?_____

_____

#98394 Herbal Medications: An Evidence-Based Review — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

_____

#94194 Prediabetes: An Opportunity to Prevent Diabetes — 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

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