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The Ohio Nurse Practice Act

ONA #2023-0000000009 (Approval valid through 01/17/2025)
*1 Contact Hour for Category A**

Audience
This one contact hour Category A course is designed for all Ohio nurses.

Course Objective
The purpose of this course is to provide basic knowledge of the current Ohio Revised Code and the Ohio Administrative Code for nurses in order to increase compliance and improve patient care. Ohio nurses are legally obligated to be aware of standards that govern professional accountability. Information contained in this course is not intended to be used in lieu of lawful guidelines, but as a learning tool that increases the understanding of some regulations as they apply to nurses who are licensed within the state of Ohio.

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

1. Identify the organization and mission of the Ohio Board of Nursing.
2. List the components of the nursing process, as related to the practice of registered nurses and licensed practical nurses in the state of Ohio.
3. Recognize the importance of safe nursing practice.
4. Identify nursing violations that may result in the revocation of a license.

Faculty
Sally Anthony, MS, RN, Paralegal, received her paralegal certification in 1992. She received her master's degree in health education in 1982 and has been a registered nurse for more than 30 years. As a medical-legal consultant for more than 20 years she has worked with attorneys on medical malpractice cases and personal injury cases. In addition, she donates her time to work with legal interns at the Gonzaga University Legal Assistance program. Her nursing practice has taken place in a variety of clinical settings that are as diverse as post-open heart advanced care and child legislative testimony. She had also worked as a health educator, consulting nurse, psychiatric/chemical dependency assistant nurse manager, regional poison center director and medical-surgical nurse. She currently works as a medical-legal consultant and is an award winning medical writer.

Faculty Disclosure
Contributing faculty, Sally Anthony, MS, RN, Paralegal, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner
Sharon Cannon, RN, EdD, ANEF

**Category A refers to a continuing education activity that was approved by an Ohio Board of Nursing Approver. Only education regarding the Ohio Nurse Practice Act and the rules of the Ohio Board of Nursing must be Category A. All remaining hours may be completed through an ANCC-accredited provider.*

Senior Director of Development and Academic Affairs
Sarah Campbell

Division Planner/Director Disclosure
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Reading Committee
Karen Brindza, LPN

Reading Committee Disclosure
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Special Approvals
This continuing education activity was approved by the Ohio Nurses Association, an Ohio Board of Nursing approver. (OBN-001-91).

Approval valid through January 17, 2025. Assigned ONA #2023-0000000009, 1 contact hour for Category A.

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

INTRODUCTION

The Nurse Practice Act dates back to 1915, when the Ohio Legislature sought to regulate and reform nursing in the state with regard to education, competence, and standards of practice, and although it was initially met with resistance by healthcare professionals, the intent was for patients to receive a higher level of care [9]. Today, registered nurses (RNs), licensed practical nurses (LPNs), and advanced practice registered nurses (APRNs) in the state of Ohio are legally bound to "practice in accordance with acceptable and prevailing standards of safe nursing care" established and codified as a result of the Act [4].

The Ohio Board of Nursing, as an agency of the state, is charged with the responsibility of administering and enforcing Chapter 4723 of the Ohio Revised Code (ORC), the legislation that arose from the Nurse Practice Act and which established the Board of Nursing. The practice of registered nurses, advanced practice registered nurses (certified nurse practitioners, clinical nurse specialists, certified nurse midwives, and certified registered nurse anesthetists), licensed practical nurses, dialysis technicians, medication aides, and community health workers is regulated by the Board, which has set forth administrative rules in Chapter 4723 of the Ohio Administrative Code (OAC). According to state law, the Ohio Board of Nursing is required to review their Code at least once every five years. Thus, it becomes the prudent practice for each Ohio nurse to become familiar with and periodically review the basic standards of practice and the laws and rules that govern the major areas of practice for both the RN and LPN. This course will acquaint nurses with the basics of Chapter 4723, which is the legal parameter for evaluating and disciplining nurses within this state.

BOARD ORGANIZATION AND MISSION

What is the Ohio Board of Nursing's mission?

The Ohio Board of Nursing consists of 13 members and includes eight registered nurses (at least two of which must be authorized to practice as an advanced practice registered nurse), four licensed practical nurses, and one consumer member that represents the interests of consumers of health care [2]. A president and vice-president are elected from among the members; these positions are one-year terms. Board members serve four years, commencing on the 1st day of January and ending on the 31st day of December. In addition, the Board employs a full-time Executive Director who is a registered nurse.

The Board's mission is "to actively safeguard the health of the public through the effective regulation of nursing care" [1]. The Board evaluates reported deviation from standards with relation to intent, pattern, and circumstance. After evaluating a possible violation, a nurse is adjudicated through due process action. The Board may revoke or place restrictions on the nurse's license, reprimand and levy a fine, or take no action when standards have been breached with regard to nursing process, patient safety, competent practice, or proper delegation.

STANDARDS OF PRACTICE

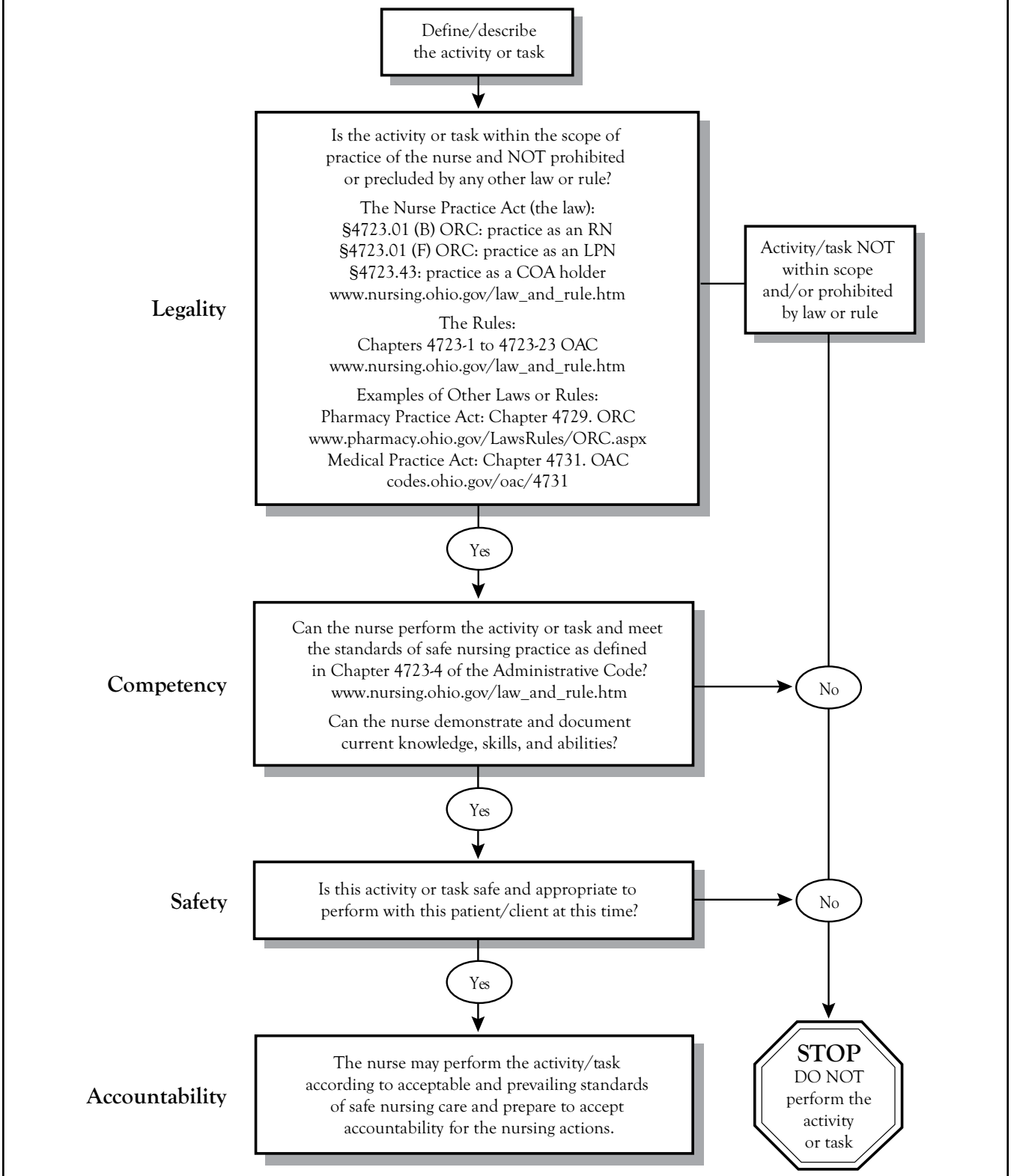
The basic standards of competent practice directly impact how both RNs and LPNs provide care [2]. Not only must a nurse possess the knowledge of lawful and current care standards, but the knowledge must be demonstrated through consistent practice and intervention to prevent unauthorized, inappropriate, erroneous, illegal, contraindicated, or intentional nonperformance of care. The Board has provided a tool for scope of practice decision making (***Figure 1***) [8]. This tool may be helpful in determining if an activity or task is within the defined scope of practice.

STANDARDS FOR APPLYING THE NURSING PROCESS AS A REGISTERED NURSE

According to the Ohio Nurse Practice Act, the practice of nursing as a registered nurse means "providing to individuals and groups nursing care requiring specialized knowledge, judgment, and skill derived from the principles of biological, physical, behavioral, social, and nursing sciences" [2]. The ORC further defines the scope of practice of a registered nurse as [2]:

- Identifying patterns of human responses to actual or potential health problems amenable to a nursing regimen
- Executing a nursing regimen through the selection, performance, management, and evaluation of nursing actions
- Assessing health status for the purpose of providing nursing care
- Providing health counseling and health teaching
- Administering medications, treatments, and executing regimens authorized by an individual who is authorized to practice in this state and is acting within the course of the individual's professional practice
- Teaching, administering, supervising, delegating, and evaluating nursing practice

RN AND LPN DECISION-MAKING MODEL:
OHIO BOARD OF NURSING



Source: Ohio Board of Nursing. RN and LPN Decision Making Model. Available at https://nursing.ohio.gov/resources-for-practice-and-prescribing/resources/02-rn-and-lpn-decision-making-model. Reprinted with permission from the Ohio Board of Nursing. *Figure 1*

In conjunction with his or her knowledge, the RN uses the nursing processes of assessment, analysis, planning, implementation, and evaluation to perform duties as outlined by the OAC [3]:

- Assessment of health status involves collecting and documenting data from the patient, family members, significant others, and other members of the healthcare team. The RN may direct or delegate the performance of data collection.
- Analysis of individual patient needs should utilize skills and reasoning, including identification, organization, assimilation, and interpretation of data to establish, accept, or modify a nursing diagnosis. The patient's health status and nursing diagnosis must be reported to other members of the healthcare team.
- Planning for care involves the development, establishment, maintenance, or modification of the nursing plan of care consistent with current nursing science, including the nursing diagnosis, desired patient outcomes or goals, and nursing interventions. It must be communicated to other team members in a timely fashion to allow for input and modification or implementation.
- Implementation involves executing the nursing regimen; implementing the current plan of care; providing nursing care within the RN's documented scope of education, knowledge, skills, and abilities; assisting and collaborating with other healthcare providers in the care of the patient; and delegating appropriate nursing tasks. In some cases, this also involves collaboration in the administration of care that has been ordered by a licensed practitioner.
- Evaluation of the patient's response to nursing treatment is a critical component of nursing practice. Progress toward expected outcomes should be documented. RNs should also reassess the patient's health status and establish or modify any aspect of the nursing plan. After performing the evaluation, the RN must communicate the patient's response to others who are involved in the patient's care and seek medically prescribed modification when indicated by prudent nursing judgment.

STANDARDS FOR APPLYING THE NURSING PROCESS AS A LICENSED PRACTICAL NURSE

What is the role of the LPN in the nursing process?

Under the Nurse Practice Act, practicing as an LPN is defined as providing to individuals and groups nursing care requiring basic knowledge, judgment, and skill derived from the principles of biological, physical, behavioral, social, and nursing sciences at the direction of a licensed physician, dentist, podiatrist, optometrist, chiropractor, or registered nurse [2].

When the LPN is properly trained and supervised, this care may consist of special tasks. The practical nurse contributes to the assessment, planning, implementation, and evaluation of care while communicating information to others [3].

The knowledge and ability of the LPN are significant contributions to the assessment of the effect of medical orders and nursing diagnoses. Therefore, it is important that this information, whether objective or subjective, be imparted in a careful and timely fashion to the rest of the healthcare team.

These data will be interpreted by an RN or other certified practitioner for the purpose of planning an individualized system of care for each patient. Notification of the possible need for modification of a new or ongoing plan or emergent intervention is a critical duty.

The LPN is then involved in implementing the nursing plan of care in an accurate and timely manner, which may include providing nursing interventions; collecting and reporting patient data as directed; administering medications and treatments prescribed by an individual who is authorized to practice in this state and is acting within the course of the individual's professional practice; providing basic nursing care as directed; collaborating with other nurses and other members of the healthcare team; and delegating nursing tasks as directed, including medication administration, in accordance with the law.

While contributing to ongoing care in a skillful and efficacious manner, the LPN is able to observe patient outcomes and provide further evaluation reports to the directing RN or healthcare provider and documentation for members of the treatment team.

ADVANCED PRACTICE REGISTERED NURSES

A registered nurse with a current, valid license to practice nursing in Ohio may use a title or initials denoting specialty certification in a particular area of specialty in nursing granted by a national certifying organization [3]. These nurses are considered APRNs and include certified registered nurse anesthetists, clinical nurse specialists, certified nurse-midwives, and certified nurse practitioners. An APRN may provide nursing care that requires knowledge and skill obtained from advanced formal education and clinical experience.

In 2017, 2020, and 2021, the ORC was revised to clarify the rules governing licensed advanced practice nursing practice. According to ORC 4723.03, no person shall knowingly do any of the following without holding a current, valid license to practice nursing as an APRN issued under this chapter [2]:

- Engage in the practice of nursing as an advanced practice registered nurse
- Represent the person as being an advanced practice registered nurse

- Use any title or initials implying that the person is a certified nurse-midwife, certified nurse practitioner, certified registered nurse anesthetist, clinical nurse specialist, or advanced practice registered nurse authorized to practice

A nurse authorized to practice as a certified nurse-midwife, in collaboration with one or more physicians, may provide the management of preventive services and those primary care services necessary to provide health care to women antepartally, intrapartally, postpartally, and gynecologically, consistent with the nurse's education and certification, and in accordance with rules adopted by the Board of Nursing [2]. No certified nurse-midwife may perform version, deliver breech or face presentation, use forceps, do any obstetric operation, or treat any other abnormal condition, except in emergencies. However, this does not prohibit a certified nurse-midwife from performing episiotomies or normal vaginal deliveries or repairing vaginal tears.

A certified registered nurse anesthetist, consistent with the nurse's education and certification and in accordance with rules adopted by the Board, may [2]:

- With supervision and in the presence of a physician, podiatrist, or dentist, administer anesthesia and perform anesthesia induction, maintenance, and emergence
- With supervision, obtain informed consent for anesthesia care and perform preanesthetic preparation and evaluation, postanesthetic preparation and evaluation, postanesthesia care, and clinical support functions
- With supervision and in accordance with section 4723.434 of the Revised Code, engage in the activities described in division (A) of that section

The supervising physician, podiatrist, or dentist must be actively engaged in practice in Ohio. When performing clinical support functions as outlined, a certified registered nurse anesthetist may direct an RN, LPN, or respiratory therapist to provide supportive care, including monitoring vital signs, conducting electrocardiograms, and administering intravenous fluids, if the nurse or therapist is authorized by law to provide such care [2]. When practicing under the order of a certified registered nurse anesthetist, the person's administration of medication is limited to the drugs that the nurse is authorized to order or direct the person to administer.

A certified nurse practitioner may provide preventive and primary care services, provide services for acute illnesses, and evaluate and promote patient wellness within his or her nursing specialty, in collaboration with one or more physicians or podiatrists and in accordance with rules adopted by the Board [2]. A clinical nurse specialist, in collaboration with one or more physicians or podiatrists, may provide and manage the care of individuals and groups with complex health problems and provide healthcare services that promote, improve, and manage health care within the nurse's nursing specialty [2].

As of 2013, a certified nurse practitioner or clinical nurse specialist may determine and pronounce an individual's death, but only if the patient's respiratory and circulatory functions are not being artificially sustained and if, at the time the determination and pronouncement of death is made, the individual was receiving care in a nursing home, a residential care facility or home for the aging, or a county home or district home; any RN may pronounce death if the nurse was providing or supervising the individual's care through a hospice care program or any entity that provides palliative care [2; 10]. The nurse is required to notify the individual's attending physician of the determination and pronouncement of death within a period of time that is reasonable but not later than 24 hours following the determination and pronouncement of death [2; 10]. Nurses are not responsible for completing any portion of the death certificate.

In 2015, the Ohio Nurse Practice Act was amended to permit APRNs with prescriptive authority to delegate the administration of certain drugs under specified conditions [12]. In accordance with ORC 4723.48, prior to delegating the authority, nurses must assess the patient and determine that the drug is appropriate for the patient and determine that the person to whom the authority will be delegated has met the following conditions [2]:

- The authority to administer the drug is delegated to the person by an APRN who is a clinical nurse specialist, certified nurse-midwife, or certified nurse practitioner.
- The drug is not listed in the formulary (established under section 4723-9-10 of the Revised Code), is not a controlled substance, and is not to be administered intravenously.
- The drug is to be administered at a location other than a hospital inpatient care unit; a hospital emergency department or a freestanding emergency department; or an ambulatory surgical facility.
- The person has successfully completed education based on a recognized body of knowledge concerning drug administration and demonstrates to the person's employer the knowledge, skills, and ability to administer the drug safely.
- The person's employer has given the APRN access to documentation, in written or electronic form, showing that the person has met these conditions.
- The APRN is physically present at the location where the drug is administered.

As of 2016, certified nurse practitioners, clinical nurse specialists, and certified nurse-midwives are authorized to treat their patients' sexual partners for certain diseases without having examined the partner, in accordance with ORC 4723.481 [13].

Overdose-Reversal Drugs

Effective December 2020, an APRN who is designated as a clinical nurse specialist, certified nurse-midwife, or certified nurse practitioner and who has established a protocol that meets the requirements of the law may authorize one or more other individuals to personally furnish a supply of overdose-reversal drug (e.g., naloxone) pursuant to the protocol to an individual who there is reason to believe is experiencing or at risk of experiencing an opioid-related overdose and/or a family member, friend, or other person in a position to assist an individual who there is reason to believe is at risk of experiencing an opioid-related overdose [2]. The written protocol should include [2]:

- A description of the clinical pharmacology of overdose-reversal drugs
- Precautions and contraindications concerning furnishing overdose-reversal drugs
- Any limitations concerning the individuals to whom overdose-reversal drugs may be furnished
- The overdose-reversal drug dosage that may be furnished and any variation in the dosage based on circumstances
- Labeling, storage, record keeping, and administrative requirements
- Training requirements that must be met before an individual will be authorized to furnish overdose-reversal drugs
- Any instructions or training that the authorized individual must provide to an individual to whom overdose-reversal drugs are furnished

APRNs authorized to personally furnish overdose-reversal drugs may do so without having examined the individual to whom it may be administered.

STANDARDS OF NURSING PRACTICE PROMOTING PATIENT SAFETY

Providing safe patient care requires the nurse to take what steps?

In addition to competency, licensed nurses have the responsibility to provide safe patient care. This requires the nurse, at all times, to [4]:

- Display applicable identification indicating licensure as a registered nurse or licensed practical nurse, including area of practice (e.g., certified nurse-midwife).
- Identify to each patient or healthcare professional the nurse's title or initials when engaged in nursing practice through telecommunications.
- Delegate a nursing task, including medication administration, only in accordance with Board rules.
- Report and document nursing assessments or observations in a complete, accurate, and timely manner. This includes care provided by the nurse for the patient, and the patient's response to that care.
- Report to the appropriate practitioner errors in or deviations from the current valid order.
- Refrain from falsifying, or concealing by any method, any patient record or any other document prepared or utilized in the course of, or in conjunction with, nursing practice. This includes, but is not limited to, case management documents or reports or time records, reports, and other documents related to billing for nursing services.

The OAC 4723-4-06 states that all licensed nurses must take measures to promote a safe environment for each patient. Specifically, this includes delineating, establishing, and maintaining professional boundaries with each patient. When providing direct nursing care to a patient, licensed nurses should treat each patient with courtesy, respect, and with full recognition of dignity and individuality. During examination or treatment and in the care of personal or bodily needs, privacy should be respected and given. Licensed nurses should not engage in behavior that causes or may cause physical, verbal, mental, or emotional abuse to a patient [5].

Licensed nurses are strictly prohibited from misappropriating patient property or becoming inappropriately involved in personal relationships. This includes [4]:

- Engaging in behavior to seek or obtain personal gain at the patient's expense or behavior that may reasonably be interpreted as such an attempt
- Engaging in behavior that constitutes or may reasonably be interpreted as inappropriate involvement in the patient's personal relationships

This delineation extends to engaging in inappropriate sexual relationships with patients. A licensed nurse shall not [4]:

- Engage in sexual conduct with a patient
- Engage in conduct in the course of practice that may reasonably be interpreted as sexual
- Engage in any verbal behavior that is seductive or sexually demeaning to a patient
- Engage in verbal behavior that may reasonably be interpreted as seductive or sexually demeaning to a patient

Patients are always presumed incapable of giving free, full, or informed consent to sexual activity with the nurse.

In 2014, the General Assembly of the State of Ohio passed HB 341, which mandates query of the Ohio Automated Rx Reporting System (OARRS) under specified circumstances [11]. This bill requires all APRNs who hold certificates to prescribe (CTP) and who prescribe opioid analgesics or benzodiazepines to register with OARRS by January 1, 2015. In addition, beginning April 1, 2015, a 12-month query of OARRS must be completed (and documented) prior to "initially prescribing or personally furnishing an opioid analgesic or benzodiazepine" [11]. Regular monitoring of these patients is also required if treatment continues for more than 90 days. CTP holders who are in violation of these laws are subject to disciplinary action.

Effective December 2018, the rules governing prescribing have been modified; the rules were revised again in 2021 [2]. A clinical nurse specialist, certified nurse-midwife, or certified nurse practitioner may prescribe any drug or therapeutic device in any form or route of administration if the ability to prescribe the drug or therapeutic device is within the scope of practice in the APRN's specialty area and the prescription is consistent with the terms of a standard care arrangement entered into with a physician [2]. The drug or therapeutic device must not be one excluded by the formulary (available at https://nursing.ohio.gov/wp-content/uploads/2019/08/Exclusionary_Formulary5.3.pdf). Prescribing authority also requires that a valid prescriber-patient relationship exists. This relationship may include, but is not limited to [2]:

- Obtaining a relevant history of the patient
- Conducting a physical or mental examination of the patient
- Rendering a diagnosis
- Prescribing medication
- Consulting with the physician when necessary
- Documenting these steps in the patient's medical records

APRNs may also prescribe or personally furnish a drug to up to two sexual partners of a patient [2].

In 2016, Ohio legalized the use of medical marijuana for qualifying conditions. However, nurses may only possess or administer medical marijuana if they are registered with the Pharmacy Board as a registered caregiver for a specific registered patient [16; 17].

Elder Abuse

As of September 2018, nurses, dialysis technicians, and employees working in nursing homes, residential care facilities, home health, hospitals, community mental health, and other work sites who have reasonable cause to believe that an adult is being abused, neglected, or exploited, or is in a condition that is the result of abuse, neglect, or exploitation, are required to immediately report such belief to the Department of Jobs and Family Services in the county where the adult resides [14; 15]. Ohio also has a statewide, toll-free number for reporting elder abuse: 1-855-OHIO-APS (855-644-6277). Reports can be made by phone, in writing, or in person.

Telehealth

In early 2020, in response to the COVID-19 crisis, the Ohio Board of Nursing issued guidance regarding the safe and appropriate use of technology for the provision of nursing care. The Board states that "nurses may use any type of telecommunication equipment to examine and assess patients; provide patients and family health teaching and health counseling (by the RN); patient teaching (by the LPN); and convey information to authorized healthcare providers and other members of the healthcare team" [18]. All nurses engaged in telehealth should remember that they are expected to practice within their scope of practice and with consideration of privacy, confidentiality, and documentation.

Nurses may use synchronous or asynchronous technology to provide telehealth services to a patient during an initial or annual visit if the appropriate standard of care is satisfied [2]. However, if appropriate, nurses may choose to deny a patient telehealth services and, instead, require the patient to undergo an in-person visit.

ORC 4743.09 requires that nurses providing telehealth services comply with all requirements under state and federal law regarding the protection of patient information [2]. This includes provisions for the protection of usernames, password, and any electronic communications between the professional and a patient.

NURSING LICENSURE COMPACT

In 2021, Ohio Senate Bill 3 Nurse Licensure Compact (NLC), was passed by the legislature and signed by the Governor [19]. This law went into effect January 1, 2023, and allows Ohio RNs and LPNs to practice in other compact states if they are issued a multistate license by the Ohio Board of Nursing [2]. The Board began issuing multistate licenses in January 2023 [19].

DISCIPLINARY ACTIONS

Which violations may result in the revocation or suspension of a nursing license?

A nurse who commits fraud through misrepresentation or deception when applying for renewal of a nursing license may have his or her license revoked by the Board. The Board may also deny, revoke, suspend, or place restrictions on any nursing license; reprimand or otherwise discipline a holder of a nursing license; or impose a fine of not more than $500 per violation for a multitude of reasons. Violations can be grouped into general areas; the following is not meant to be an inclusive account of every type of infringement [6]. (Please refer to Section 4723.28 of the Ohio Revised Code for a complete list of violations.)

Engaging in criminal activity, either in the course of practice or outside of a practice setting, may be grounds for disciplinary action. Criminal activity is defined as being convicted of or pleading guilty to a misdemeanor or felony. In the case of a misdemeanor committed in the course of practice, there may be a finding of "eligibility for a pretrial diversion or similar program or for intervention in lieu of conviction" [6]. The Board may impose sanctions for being convicted of a felony in relation to gross immorality or moral turpitude, the illegal sale of drugs or therapeutic devices, or committing a crime outside of the jurisdiction of the state that would constitute a felony or misdemeanor in the state of Ohio [6].

Any action that causes impairment is also grounds for sanction by the Board. This includes self-administering dangerous drugs without a prescription and habitual indulgence of habit-forming drugs, alcohol, or other chemical substances. A physical or mental disability may also impair the nurse's ability to practice according to acceptable and prevailing standards of safe nursing. If a nurse's license has been revoked due to mental illness or incompetence, the Board may reinstate the license upon proof of competence through adjudication of a probate court [6].

Other violations include assaulting or causing harm to a patient, depriving a patient of the means to summon assistance, and using intentional misrepresentation or material deception to obtain money and/or anything of value in the course of practice. The nurse who fails to establish and maintain professional boundaries with a patient or engages in sexually inappropriate behavior, physically or verbally, is also eligible for disciplinary action [6].

Disciplinary action may also result from violating safety precautions. Safety violations include the failure to use universal blood and body fluid precautions and the failure to practice in accordance with acceptable and prevailing standards of safe nursing care. Engaging in activities that exceed the scope of practice of the licensee is deemed unsafe. In addition, aiding and abetting the practice of nursing by a person who does not hold a license is grounds for sanction by the Board [6]. Effective December 2020, APRNs who are clinical nurse specialists, certified nurse-midwives, or certified nurse practitioners who fail to comply with the terms of a consult agreement entered into with a pharmacist may be sanctioned [6].

The Ohio Board of Nursing has established the Patient Safety Initiative in collaboration with nursing employers with the goal of increasing patient safety through effective reporting, remediation, modification of systems, and accountability [7]. The Initiative established the Practice Intervention and Improvement Program, the Board's confidential alternative to discipline program for eligible licensees. The program establishes a structured remedial education and monitoring program to document that the participant's practice deficiency has been corrected [7]. When a complaint is filed, Board staff present the case to the Board Supervising Member for Disciplinary Matters for review and disposition [7]. Many complaints do not result in public disciplinary action, but remain confidential and closed unless subsequent violations are reported. In keeping with due process, as defined in Chapter 119 of the Ohio Revised Code, the nurse is provided the opportunity for a hearing, the outcome of which may be to deny, revoke, suspend, or place restrictions on the license; reprimand, fine, or otherwise discipline the nurse; or take no action [6].

CASE STUDIES

CASE STUDY 1: IV FLUID ADMINISTRATION

Nurse B has been an RN for almost 20 years. One night, there is an unusually heavy caseload at the emergency care facility where she works. One patient at the facility is 32 years of age and presented with dehydration and heat stroke. The patient is showing signs of altered consciousness and has a rapid heartbeat and low blood pressure. Nurse B is one of two RNs on duty, so the task of starting the patient on a 0.9% normal saline IV has fallen to Nurse W, an LPN who began administering intravenous therapies approximately two weeks ago. With the initial assessment and plan of care complete, Nurse B decides to leave Nurse W to start the rehydration drip unsupervised because he seems confident in his ability to administer IV fluids; this frees her up to assist patients with multiple trauma. Although Nurse B has not personally supervised Nurse W during IV administration, she knows that this LPN is quite competent in other nursing tasks. When Nurse W offered to administer the saline, he confirmed that he has completed a Board-approved IV therapy course pursuant to ORC 4723.17. Additionally, Nurse B states that she will check back soon, and if any problems should arise, that she is to be notified immediately.

Rationale and Comments

The task of administering IV saline is within a LPNs scope of practice and is within the rules governing LPNs (Section 4723.17.03B of the Ohio Revised Code). With the patient assessment completed and the results of the nursing task reasonably predictable, the RN may be generally correct in directing an LPN to complete this procedure. She was also correct in reminding the LPN to notify her pending a change in patient status and that she would return to check on the patient. However, Nurse W is relatively new to administering IV fluids, and it is unclear whether he has attempted to establish a line on a dehydrated patient with the possibility of collapsed veins. Before directing Nurse W, Nurse B should have evaluated whether an improperly performed task could cause a life-threatening consequence. In this case, an improperly placed IV line or failure to access a vein may lead to a worsening of the patient's condition. Furthermore, because supervision was not available at the time and because Nurse B failed to ascertain from a supervisor whether Nurse W was competent in IV administration to dehydrated individuals, directing Nurse W to complete the task was not in the best interest of the patient.

CASE STUDY 2

Nurse A is an RN, 37 years of age, working in a busy university hospital's cardiac intensive care unit who possesses a good deal of first-hand experience monitoring anticoagulant therapies. An obese male patient, 65 years of age, is admitted early in the morning with acute bilateral deep vein thrombosis in his femoral veins, confirmed by ultrasonography; the patient has a history of chronic heart failure, and his international normalized ratio (INR) is 0.5.

Attending Physician G, an intern, has ordered the patient to be started on an initial dose of warfarin 5 mg and enoxaparin. The patient care plan involves daily monitoring of INR and possibly titrating the warfarin dose to achieve a therapeutic INR of 2.5. For three days the patient's INR has been rising slowly to 1.5 on dosages of 7.5 mg and then 10 mg of warfarin. When Nurse A arrives for her shift after her day off (on day 5 of the patient's treatment), she discovers that in an attempt to speed the therapy, the intern has titrated the warfarin to 20 mg and the patient's INR is at 2.4. She knows from experience that warfarin dosages of 10 mg for heavier patients are acceptable, but 20 mg seems to be an overly aggressive approach, considering a peak effect of 36 to 48 hours, so she decides to ask Physician G to reduce the dosage back to 10 mg or to discontinue use. The physician admits not having experience administering anticoagulants and agrees to lower the dose to 5 mg.

Rationale and Comments

As a member of the healthcare team, it is a registered nurse's duty to contribute his or her knowledge, experience, and observations to improve patient safety and outcomes. Pursuant to OAC Section 4723-4-03-E, nurses should implement a current valid order unless they feel the order is inaccurate; not properly authorized; not current or valid; harmful or potentially harmful to a patient; or contraindicated by other documented information. In this instance, the nurse's judgment dictated that implementing the current order of administering warfarin 20 mg had serious potential to be harmful to the patient. It is important to remain vigilant regarding patient safety and to document and voice concerns regarding the patient's individualized system of care.

CONCLUSION

It is the responsibility of the Ohio Board of Nursing to enforce the laws and rules regulating the practice of nursing as the law is currently stated and not how individuals may wish the law to be. However, as nurses are affected by these rules and regulations, they have the responsibility to keep informed of regulatory changes and provide public comment regarding regulations. All Board meetings, held every two months, are open to the general public. In addition, the Board seeks public input through its newsletter, *Momentum*. For those individuals with special concerns, the Board may hold special forum sessions. For more information please contact the Board at 614-466-3947 or https://nursing.ohio.gov. Practice issues or questions may be sent directly to the Board by email to practiceRNandLPN@nursing.ohio.gov or practiceAPRN@nursing.ohio.gov.

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

Counseling Patients at the End of Life

Audience
This course is designed for all members of the interprofessional team responsible for supporting patients at the end of life.

Course Objective
The purpose of this course is to provide physicians, nurses, physician assistants, and allied health professionals with the knowledge and strategies necessary to best assist patients to seek and receive optimal end-of-life care.

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

1. Define palliative and end-of-life care.
2. Outline the role of health and mental health professionals in end-of-life counseling.
3. Identify psychological concerns present at the end of life.
4. Discuss key components of end-of-life conversations.
5. Analyze mental health interventions that can be incorporated into end-of-life care and bereavement.
6. Describe practical, ethical, and legal issues that can arise in the provision of end-of-life care.
7. Examine the impact of culture and culturally competent care on end-of-life decisions and support.

Faculty
Lisa Hutchison, LMHC, has more than 20 years of experience providing individual and group counseling with adults. She specifically focuses on teaching assertiveness, stress management, and boundary setting for empathic helpers. Ms. Hutchison graduated from the University of Massachusetts, Boston, with a Master's degree in education for mental health counseling.

Faculty Disclosure
Contributing faculty, Lisa Hutchison, LMHC, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner
Margo A. Halm, RN, PhD, ACNS-BC

Senior Director of Development and Academic Affairs
Sarah Campbell

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

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

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

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

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About the Sponsor

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

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

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

INTRODUCTION

End-of-life decisions can be complex and challenging. Health and mental health professionals can help with their expertise, whether it is for the person facing death, their family, surrogate decision makers, or caregiver. It is vital for health and mental health professionals to learn when and how to include end-of-life discussions into their sessions, assist with decision making and planning, and learn the differences between palliative and end-of-life care.

DEFINING END-OF-LIFE CARE

What is the goal of palliative care?

The terms palliative care and end-of-life care often are used interchangeably, but there are some differences. The goal of palliative care is to improve the quality of life of patients and their families when faced with life-threatening illness. This is achieved through the prevention and relief of suffering and treatment of pain and other physical, psychosocial, and spiritual problems [1]. Palliative care includes measures used to achieve comfort for the patient. Palliative care can be provided at any stage of a serious illness, including as early as the time of diagnosis. Unlike patients receiving end-of-life care, those receiving palliative care may still be pursuing curative treatment [2].

End-of-life care (which may include palliative care) is generally defined as care that is provided to seriously ill patients who have a prognosis of six months or less. It is care intended for the last few weeks or months of a patient's life. End-of-life care can be provided in a variety of settings, including the patient's home, nursing homes or assisted living facilities, or inpatient hospice facilities [2]. End-of-life care is a multidisciplinary team approach toward "whole person care." It is intended for people with advanced, progressive, incurable, or life-limiting illness to enable them to live as well as possible before they die [3]. This course will focus on end-of-life care.

THE ROLE OF HEALTH AND MENTAL HEALTH PROFESSIONALS IN END-OF-LIFE COUNSELING

Which professionals can provide end-of-life counseling?

The transition of care from eliminating or mitigating illness to preparing for death can be difficult for patients, families, and caregivers, and it can be equally difficult for healthcare professionals, who are expected to meet the physical and emotional needs of dying patients and their families [4]. By understanding the experiences of the dying patient, health and mental health professionals can best support the unique needs of each patient and the patient's loved ones as well as

self and other members of the patient's healthcare team [4; 5; 6; 7]. Mental health professionals are uniquely positioned to address the cognitive, mental, and emotional needs that arise during this period of life-limiting illness [8; 9]. They work to normalize emotions during a difficult time; provide spiritual support; educate about normal physical, emotional, and social changes; and assist in managing practical problems. They also may develop relationships with survivors to provide a continuity of care following the patient's death. Health and mental health professionals work in a variety of settings that address end-of-life care, including health agencies, hospitals, hospice and home care settings, nursing homes, and courts [10].

Both end-of-life and palliative counseling are services provided by clinicians who work with the terminally ill. End-of-life counseling helps patients struggling with death or families struggling with the death of a loved one and may be provided by counselors, therapists, social workers, psychologists, critical care nurses, physicians, hospice workers, and others trained in working with emotions related to death, dying, grief, and bereavement [8].

Health and mental health providers provide services to diverse individuals in a variety of settings, including end-of-life settings, as part of an interprofessional team. In the end-of-life setting, clinicians help dying patients prepare for death with education and supportive therapeutic interventions that address the patient's physical, emotional, social, spiritual, and practical needs [10]. They also help patients and their families navigate the many challenges associated with dying, including end-of-life planning; managing stresses associated with life-limiting illness; assessing patients to develop interventions and treatment planning; advocating for patients' treatment plans; overcoming crisis situations; and connecting them with other support services [11; 12]. Life-limiting illness is mentally taxing and can exacerbate or incite symptoms of anxiety, depression, and trauma and make manifest complex presentations of cognitive decline. Providers can help differentiate between trauma symptoms, mental illness, or medical decline. Reducing mental health symptoms can help patients engage more meaningfully, including in the participation of end-of-life decisions [9]. A cohesive, standardized approach to end-of-life care addresses issues related to the patient, family, caregivers, and the team of healthcare professionals involved in providing care [12].

PSYCHOLOGICAL CONCERNS FOR PATIENTS AT THE END OF LIFE

Psychological suffering is a universal experience for patients at the end of life. It exists on a continuum and has many sources, including grief over anticipated loss or worry about unresolved issues. It is important to assess and differentiate the major types of distress in the dying patient and among their families to effectively treat these sources of suffering.

LIFE-CYCLE ISSUES/RELATIONSHIPS

Psychological responses to the news of a life-limiting illness will vary according to the patient's developmental stage. The young adult, about to become independent, might struggle with being thrust back into dependence upon parents or other adult figures. Parents of young children with life-limiting illness often are consumed with what and how much to tell their ill child, the impact of the child's illness on other siblings, and how to cope with the loss of the child's future. Worries about a spouse or partner are a common concern for older adults. They may feel cheated out of the expected rewards of a life of hard work. Worries about family members are a major issue for most patients at the end of life [13]. One study found that 92% to 97% of patients rated as extremely or very important "feeling appreciated by my family," "saying goodbye to people closest to me," "expressing my feelings to family," and "knowing that my family will be all right without me" [14]. Caregivers of patients with terminal illness also experience significant strains (e.g., adverse impact on work and finances) [15]. Awareness of these life-cycle and relationship issues can help the clinician listen for and inquire about concerns and emotions, normalize patient responses, and explore areas of distress [13].

MEANING AND IDENTITY

Illness comes with practical and emotional challenges that are unique to each patient. The clinician who understands what the illness means to the patient can identify specific concerns, address fears, provide reassurance, and help the patient make plans. Providing patients with the opportunity to share what their illness means can be therapeutic in and of itself [13]. Some patients state that finding meaning in illness is derived from the belief that their life has a purpose that extends beyond self. Others find that meaning enhances their ability to cope with their illness. Still others experience a loss of meaning when faced with life-limiting illness. The patient's ability to find and maintain a sense that life has purpose and meaning is associated with the ability to tolerate physical symptoms of the illness and protect against depression and a desire for hastened death [13]. Meaning and hope are closely allied in patients at the end of life, and hopes for the future reflect the patient's priorities.

Maintaining a sense of self is a high priority among patients with life-limiting illness, yet serious illness has a profound impact on patient self-identity. The physical and psychological losses (e.g., loss of feeling whole, loss of independence, loss of control) present major challenges to the patient's emotional health. Control and independence often are combined in the literature to mean the patient's dignity, or the "quality or state of being worthy, honored, or esteemed" [13]. Preservation of this dignity should be a primary concern of end-of-life care practitioners.

COPING AND STRESS

What is a possible negative effect of denial in patients at the end of life?

Confronting a life-limiting illness causes patients to make psychological adjustments to preserve equilibrium. Coping responses can include seeking information about the illness, staying busy to avoid thinking about the illness, resigning one's self to the illness, examining alternatives, and talking about feelings. Effective coping occurs when the patient is able to use active problem-solving strategies. Yet, as illnesses progress, patients' ability to perform cognitive tasks can decline. Some patients cope by defending against or denying the reality of their illness to fend off acute emotional distress. The dynamic tension between coping and defending/denying causes most patients to use a combination of these responses [13]. While denial is a powerful mechanism that helps preserve psychological equilibrium, it can have many negative effects, including refusal to accept death; lost trust in the healthcare team; focus on unrealistic treatment goals; and failure to make legal, financial, and healthcare arrangements [13]. Life-limiting illness represents a major adaptational challenge to patients' learned coping mechanisms. Psychosocial stressors enhance the likelihood that a patient will become depressed. Practical stressors (e.g., relationships, work, finances, legal matters) also can impact patients' ability to cope with their illness. Economic circumstances have been found to be a major stressor for patients and their families, often resulting in a decline in family economic well-being [13]. In one study, 20% of family members of seriously ill adult patients had to make a major life change (including quitting work) to care for their loved one; up to 31% of families lost all or most of their savings while caring for their ill loved one [14].

Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) may first emerge, re-emerge, or worsen as individuals approach the end of life and may complicate the dying process. Unfortunately, lack of awareness of the occurrence and/or manifestation of PTSD at the end of life can result in it being unaddressed in these patients. Even if PTSD is properly diagnosed, traditional evidence-based, trauma-focused treatments may not be feasible or advisable for patients at the end of life, as they often lack the physical and mental stamina to participate in traditional psychotherapy [16]. Many therapies for PTSD require a longer window of treatment than a typical hospice period. Providers can tailor treatment for short-term interventions or use approaches such as the Stepwise Psychosocial Palliative Care (SPPC) model. The SPPC model is a multidimensional approach, integrating environmental, problem-solving, and other psychosocial interventions with patient advocacy in a patient-centered, time-sensitive manner. It incorporates techniques drawn from evidence-based approaches to PTSD, deploying them in a stage-wise manner appropriate for patients at the end of life [17]. Debriefing interventions have been widely used to treat PTSD and the psychological sequelae of traumatic events, and these approaches can be appropriate in the end of life. Further, antidepressant, antianxiety, and antipsychotic agents may be used to manage intense symptoms. Support groups and psychoeducational approaches are also common approaches, but evidence of their effectiveness in this setting is lacking [13].

ANTICIPATORY GRIEF

Anticipatory grief is the experience of grieving the loss of a patient or loved one in advance of their death [18]. It is a response to impending loss of life, identity, function, hopes, and future plans and is associated with anxiety, depression, hopelessness, and strained communication [19]. Other intense emotions, such as fear and panic, can appear as a result of unexplained symptoms and uncertainties regarding treatment [20]. One study evaluated anticipatory grief in 57 family members of patients with terminal illness receiving palliative care services [18]. Elevated anticipatory grief was found in families characterized by relational dependency, lower education, and poor grief-specific support. These families also experienced discomfort with closeness and intimacy, neuroticism, spiritual crisis, and an inability to make sense of the loss [18]. Patients, families, caregivers, and clinicians all can experience anticipatory grief. Several factors (e.g., spiritual beliefs, quality of relationships, attitudes of close others or colleagues/peers) can influence the anticipatory grief toward either positive or negative outcomes [21].

As a core component of psychological flexibility, acceptance is beneficial in situations in which individuals have little or no control over circumstances, such as when faced with a life-limiting illness. Acceptance becomes an active process wherein the patient acknowledges and opens up to their situation in order to make the most of their remaining time. Although acceptance shares a strong relationship with anticipatory grief, depression, and anxiety, it is independent of anxious and depressive symptomatology and more likely to predict the level of anticipatory grief than anxiety or depression. A higher degree of acceptance is associated with lower anticipatory grief in patients in palliative care [19]. When anticipatory grief is an expression of past or current trauma, it may develop into complicated grief if left untreated. A thorough assessment is warranted to determine if the grief is current or connected to unresolved trauma. Consider treating the initial trauma before the anticipatory grief. At the end of life, if time does not allow for intensive treatment, look to reduce individual trauma symptoms or grief.

ANXIETY AND FEAR

Death is an ever-present reality despite increasingly technologically advanced health systems, longer survivals, and novel curative treatments for life-threatening conditions [22]. Fear of the unknown has been described as the propensity to experience fear caused by the perceived absence of information at any level of consciousness or point of processing [23]. Fear of death and dying is common. In one study, a majority (70%)

of participants reported some, a little, or no fear of death and dying; 30% reported more severe fears [24]. A common fear in Western society is that the process of dying will be painful and prolonged and will reduce the quality of life. Other fears associated with death include [25]:

- Fear of separation from loved ones, home, and job
- Fear of becoming a burden to others
- Fear of losing control
- Fear for dependents
- Fear of pain or other worsening symptoms
- Fear of being unable to complete life tasks or responsibilities
- Fear for the fears of others (reflected fear)
- Fear of being dead

It is important that clinicians allow patients a full expression of these fears, without judgment. Patients with anxiety often cannot take in information and may ask the same questions over and over again. They may seek detailed information or not ask reasonable questions. They may be suspicious of the physician's recommendations or not ask questions because of regression or high levels of fear. They may over-react to symptoms or treatments or behave inexpressively and stoically. Their behavior may seem inconsistent and impulsive [13]. An ongoing assessment of anxiety symptoms and anxiety's various presentations is critical to maintaining the patient's mental health. Equally important is that the clinician recognize that anxiety in end-of-life care also may be the result of a pre-existing anxiety disorder or other undertreated symptoms, especially pain. A multidrug treatment regimen in the palliative care setting also can contribute to anxiety [13].

Thanatophobia

Thanatophobia is an extreme fear of death or of the dying process [26]. Fear of death as a disease entity behaves much like initial anxiety due to trauma that leads to PTSD [27]. Evidence suggests that thanatophobia is highest in patients who do not have high self-esteem, religious beliefs, good health, a sense of fulfillment in life, intimacy, or "a fighting spirit" [27]. While anxiety, depressive symptoms, and beliefs about what will happen after death can contribute to a patient's fear, death anxiety does not always follow after a diagnosis of life-limiting illness [27]. It appears to be a basic fear at the core of a range of mental disorders, including hypochondriasis, panic disorder, and anxiety and depressive disorders [28]. Antecedents of death anxiety include stressful environments and the experience of unpredictable circumstances, diagnosis of a life-threatening illness or the experience of a life-threatening event, and experiences with death and dying. Consequences of death anxiety include both adaptive and maladaptive presentations. When encountering death anxiety in a patient, assess for PTSD and the various anxiety disorders to determine whether it is anxiety-based or associated with an underlying trauma [22].

Death anxiety is a central feature of health anxiety and may play a significant role in other anxiety disorders [29]. Exposure to death-related themes has been found useful for the treatment of death anxiety [29]. A 2015 study that assessed death anxiety among patients with life-limiting cancer found that life stage, particularly having dependent children, and individual factors, such as lower self-esteem, increased patients' vulnerability to death anxiety [30]. Depressive symptoms also have been reported in health professionals who work with dying patients [31]. A 2011 study sought to assess the impact of death and dying on the personal lives of clinicians involved in end-of-life care [32]. Early life experiences and clinical exposure to death and dying helped the clinicians to live in the present, cultivate spirituality, and reflect on their own mortality and the continuity of life. Despite reporting accounts of death's ugliness, participants consistently described the end of life as a meaningful life stage [32]. Yet, not all clinicians find that working with patients at the end of life decreases their death-related anxiety, and many will require support and guidance. Burnout and death anxiety can be emotionally devastating, resulting in impaired performance that makes the goal of quality patient care almost impossible to accomplish [33]. All providers of end-of-life care should be reminded that they are not alone and that they can rely on other members of the healthcare team [34].

Education about death also may be helpful. In a 2015 study of 86 human services professionals, participation in a course on death, dying, and bereavement was shown to significantly reduce clinicians' fear of death and death anxiety [35]. In a study that included 42 nurses enrolled in death education programs, some affirmative impacts on the death distress of participants was observed [31]. Younger nurses consistently reported a stronger fear of death and more negative attitudes towards end-of-life patient care, indicating that workplace education might be beneficial [36]. One study investigated whether a brief induction of gratitude could reduce death anxiety [37]. Participants (mean age: 62.7 years) were randomly assigned into one of three conditions (gratitude, hassle, and neutral) and asked to write about a variety of life events before responding to measures of death anxiety. Participants in the gratitude condition reported lower death anxiety than those in the hassle and neutral conditions; no difference was observed between hassle and neutral conditions [37]. Even a temporary relief of death anxiety may help facilitate the making of important end-of-life decisions [37].

PAIN

Pain management is an integral part of palliative care. Pain management in end-of-life care presents unique opportunities in the patient-physician relationship [38]. In some instances, pain can be reduced when the patient has a sense of control and knows what to expect. Patients report feeling empowered by participating in treatment decisions with their physicians [39]. Pain management in children presents special challenges.

PHYSICAL DEPRESSIVE SYMPTOMS VERSUS REPLACEMENT PSYCHOLOGICAL SYMPTOMS	
Physical Symptoms	**Replacement Psychological Symptoms**
Change in appetite	Tearfulness, depressed appearance
Sleep disturbance	Social withdrawal, decreased talkativeness
Fatigue	Brooding, self-pity, pessimism
Diminished ability to think or concentrate	Lack of reactivity, blunting
Source: [43]	*Table 1*

A multidisciplinary team with an open attitude to differences, listening skills, availability, flexibility, creativity, resourcefulness, and empathy can help the child and his or her family live with the least pain possible [40]. For both adult and pediatric patients at the end life, planning for what could happen is often key. Honest, dynamic discussions about treatment goals and possible options and their respective side effects allows patients and their families to make choices that best fit their wishes [40]. Treating pain at the end of life means caring for all possible manifestations, including physical symptoms as well as psychological symptoms and reduced well-being. This can be achieved by integrating pharmacotherapy with psychosocio-spiritual interventions [41].

DEPRESSION

Evidence of hopelessness, helplessness, worthlessness, guilt, and suicidal ideation are better indicators of depression in the context of life-limiting illness than neurovegetative symptoms [42]. Yet, diagnosing and treating depression in patients with life-limiting illness remains challenging for several reasons. Typical symptoms of depression (e.g., impaired concentration, anergia, sleep disturbances) also are common symptoms of advanced mental illness, and side effects from medications commonly used at the end of life can mimic depressive symptoms. Delirium occurs in up to 90% of patients at the end of life. A mistaken diagnosis of depression in a patient with hypoactive delirium can lead to a prescription for an antidepressant or psychostimulant, which can exacerbate the delirium. To further complicate assessment, patients frequently do not report or may disguise symptoms of depression at the end of life [43]. It can also be difficult to determine if pharmacotherapy or reflective listening would be the appropriate intervention for the specific patient.

An assessment of available screening tools and rating scales for depressive symptoms in palliative care found that the tool with the highest sensitivity, specificity, and positive predictive value was the question: "Are you feeling down, depressed, or hopeless most of the time over the last two weeks?" [43]. One structured approach was found to help clinicians differentiate major depressive disorder from common physical symptoms of the patient's illness. With this approach, physical criteria for a diagnosis of major depressive disorder are replaced by psychological symptoms (***Table 1***) [43].

Some patients fear that being diagnosed with depression will cause their medical providers to stigmatize them or treat their physical symptoms less aggressively. It may then be necessary to address these issues before the patient will be willing to accept treatment for depression [42]. Left untreated, depression in seriously ill patients can be associated with increased physical symptoms, suicidal thoughts, worsened quality of life, and emotional distress. It also can impair the patient's interaction with family and erode patient autonomy [43]. Although patients with terminal illness often have suicidal thoughts, they are usually fleeting. Sustained suicidal ideation should prompt a comprehensive evaluation [42].

SUICIDALITY

Suicide is a response to two stimuli (i.e., pain and despair) that often overlap. The pain can be physical or psychological, but in either aspect, it consumes the person to the point of seeking release. Despair is the result of believing that there is no longer any hope of having a good life [44]. Uncertainty about how death will unfold and whether they will be able to cope can be intensely stressful for patients. For some, suicide may seem preferable to a protracted period of anxiety, uncertainty about the process of dying, and fear of substantial physical suffering [29]. Diagnosis of severe physical illness (e.g., chronic obstructive pulmonary disease, low-survival cancer, degenerative neurological conditions) is associated with higher suicide risk [162].

A Wish to Die

Despite research efforts to deepen understanding of why some patients with terminal illness express a wish to die, there is consensus that there is more to learn about the factors that influence such a wish [45]. A case study review of patients with terminal cancer diagnoses in palliative care sought to understand possible motivations and explanations of patients who express or experience a wish to die [45]. Intentions, motivations, and social interactions were key to understanding and analyzing a patient's wish-to-die statements. The study focused on motivations, which address the question (from the patient's perspective) of why a wish to die is present. Motivations appear to consist of three layers: reasons (the causal factors), meanings (explanatory factors), and functions (effects of the wish) [45].

Patients' motivations were not able to be explained by a single reason, and, for most, their wish to die had broader significance that reflected their personal values and moral understandings—that is, the "meaning" of their wish to die [45]. Patients reported nine types of meanings, with some appearing more frequently than others. The meanings were shaped by patients' personal experiences, cultural background, and relationships. Patients expressed that a wish to die can be a wish to [45]:

- Allow a life-ending process to take its course
- Let death put an end to severe suffering
- End a situation that is seen as an unreasonable demand
- Spare others from the burden of oneself
- Preserve self-determination in the last moments of life
- End a life that is now without value
- Move on to another reality
- Be an example to others
- Not have to wait until death arrives

Health and mental health professionals cannot properly address a patient's wish to die if the meanings of the wish remain unexplored. Meanings are loaded with moral beliefs that need to be understood and respected in communication, disease management, and care of patients and their families [45].

END-OF-LIFE CONVERSATIONS

Helping a patient appoint a surrogate decision maker is part of which step in an end-of-life conversation?

Dr. Elisabeth Kübler-Ross is credited as one of the first clinicians to formalize recommendations for working with patients with life-limiting illness. Her book, *On Death and Dying*, identified a gap in our understanding of how both patients and clinicians cope with death [46]. She wrote that it could be helpful if people could talk about death and dying as an intrinsic part of life [47]. In writing specifically about psychotherapy with the terminally ill, Dr. Kübler-Ross stated: "It is evident that the terminally ill patient has very special needs which can be fulfilled if we take time to sit and listen and find out what they are" [47].

Patients who receive the news that they do not have long to live will experience strong emotions accompanied by questions, which can be viewed as opportunities for clinicians to provide answers and open a broader discussion about the end of life. Such questions (and answers) may include [48]:

- *How long have I got?*

  Giving patients a sense of how much time is left allows them to focus on what is important to them. Answers to this question should be clear and as accurate as possible, while acknowledging that exact timeframes are impossible to know.

- *Will palliative care help?*

  When palliative care is appropriate, it supports patients and their families/caregivers by helping them to manage their physical, mental/emotional, spiritual, and practical needs. For patients at the end of life, palliative care is almost always appropriate.

- *What is a "good death?"*

  The answer to this question varies depending on each patient's attitudes, cultural background, spiritual beliefs, and medical treatments. Patients' wishes regarding where they prefer to die (e.g., at home, in hospital) also should be discussed.

- *How will I know that the end is near?*

  The answer depends on the patient and the patient's illness, but events that commonly occur during the dying process include reduced appetite, gradual withdrawal from the outside world, and sleeping more.

Data derived from a national survey of physicians, nurses, social workers, chaplains, hospice volunteers, seriously ill patients, and recently bereaved family members indicate an overwhelming preference for an opportunity to discuss and prepare for the end of life [39]. And while a majority (92%) of Americans say it is important to discuss their wishes for end-of-life care, only 32% have had such a conversation [49]. A majority of patients also prefer that a healthcare provider initiate end-of-life discussions [50]. It is important to note that these discussions do not have to wait for the end of the patient's life. The American Psychological Association has identified four time periods when health and mental health professionals can contribute to end-of-life care [51]:

- Before illness strikes
- After illness is diagnosed and treatments begin
- During advanced illness and the dying process
- After the death of the patient, with bereaved survivors

The end-of-life conversation can be divided into four simple steps [50]:

- Initiate the discussion:
  - Establish a supportive relationship with the patient and the patient's family.
  - Help the patient to appoint a surrogate decision maker.
  - Elicit general thoughts about end-of-life preferences through the use of probing questions.
- Clarify the prognosis:
  - Be direct yet caring.
  - Be truthful but sustain spirit.
  - Use simple, everyday language.

- Identify end-of-life goals:
  - Facilitate open discussion about desired medical care and remaining life goals.
  - Recognize that, as death nears, most patients share similar goals (e.g., maximizing time with family and friends, avoiding hospitalization and unnecessary procedures, maintaining functionality, minimizing pain).
- Develop a treatment plan:
  - Provide guidance in understanding medical options.
  - Make recommendations regarding appropriate treatment.
  - Clarify resuscitation orders.
  - Initiate timely palliative care, when appropriate.

Optimal end-of-life care begins with an honest discussion between clinicians and patients about disease progression and prognosis [52]. Patients and families are sensitive to verbal and nonverbal cues during these discussions. It is therefore incumbent on the healthcare team to train themselves in active listening skills, correct body language, and appropriate empathic responses in order to convey information in a clear, concise, and empathic manner [3]. Physicians also must balance their desire to honor patient wishes and autonomy against the concern of inflicting psychological harm. A 2008 study sought to determine whether end-of-life discussions were associated with fewer aggressive interventions and earlier hospice referrals [53]. The study enrolled advanced cancer patients and their informal caregivers (332 dyads) and followed them up to the time of death, a median of 4.4 months later. Quality of life and psychiatric illness was assessed in bereaved caregivers a median of 6.5 months later. Thirty-seven percent of patients reported having end-of-life discussions at baseline. These discussions were associated with lower rates of ventilation, resuscitation, intensive care unit (ICU) admission, and earlier hospice enrollment. Overall, end-of-life discussions were associated with less aggressive medical care near death, better patient quality of life, and earlier hospice referrals [53].

PATIENT WISHES

What do patients consider important in the process of preparing for the end of their lives? How do their perspectives differ from the values of family members or healthcare providers [39]? A 2015 study was conducted to define what matters most about end-of-life care [54]. Providers and administrators from 14 specialized palliative care teams were interviewed and their responses were analyzed to derive themes depicting the universal essence of end-of-life care. The most predominate theme, mentioned by almost one-half of the respondents, was that the "patient's wishes are fulfilled" [54]. Honoring patient wishes involves identifying what a patient wants through open communication and end-of-life care planning, providing education about options, providing realistic expectations, and allowing patients to have control over decision making [54]. Clinicians can regularly promote communication and education about end-of-life care issues by taking the initiative and discussing each patient's goals for end-of-life care. These goals may change over time and with illness and should be regularly re-evaluated and restated [55]. The patient's cultural and/or religious background can influence end-of-life decisions regarding comfort care and patient management, who can be present at the time of death, who will make healthcare decisions, and where the patient wants to die [56]. Encourage patients to elaborate on their wishes with prompts such as [56]:

- "In my religion, we . . ." This will help patients describe religious traditions to be observed at death.
- "Where we come from . . ." This will help patients share important customs to be observed at death.
- "In our family, when someone is dying, we prefer . . ." This will help patients describe what they hope will happen at death.

BARRIERS TO END-OF-LIFE CONVERSATIONS

Barriers to end-of-life discussions can seriously interfere with the quality of remaining life for patients with terminal illness. Barriers have been identified as originating with patients/families, with healthcare professionals, and within the structure of the healthcare system [57].

Patient-Related Barriers

Patients often avoid discussing end-of-life care with their clinicians and may conceal the full extent of what and how they are feeling, given the scope of end-of-life decisions. Family members and significant others also can complicate end-of-life conversations when they either cannot or will not discuss and accept the advanced nature of the patient's disease or the patient's preferences concerning end-of-life care, or when they overestimate the chance of cure, placing unreasonable demands upon the clinician [57].

Clinician-Related Barriers

Clinicians might avoid end-of-life discussions with their patients because they are reluctant to cause pain or be the bearers of bad news. They may lack the necessary communication training and skills, particularly in the delivery of bad news. They may focus solely on clinical parameters or have medical-legal concerns. Clinicians may fear confrontation and/or disagreement with the patient's family, particularly if they feel ill-prepared for such discussions. They may have a lack of confidence in their own judgment of their patient's true condition [57; 58]. Structured and content-based interventions are needed to ensure that critical aspects of the patient's physical, psychological, and spiritual experience are not excluded from care. For healthcare professionals who are delivering bad news, guidelines for the conversation can help give structure and enhance the confidence of the clinician (***Table 2***).

GUIDELINES FOR BREAKING BAD NEWS
Formulate a plan. Mentally rehearse the steps of the conversation.
Schedule a time for the discussion to allow all important family members and medical staff to be present.
Meet in a quiet and private setting.
Make arrangements for a professional translator if English is not the first language of the patient/family. Meet with the professional translator before the discussion to discuss expectations.
Preface bad news with a phrase to prepare the patient or family, such as "I wish the results were different, but..."
Communicate clearly and minimize use of technical language.
Let the patient's and family's reactions guide the flow of the conversation. Allow silence.
Be empathetic and acknowledge the patient's/family's emotions.
Determine the family's level of understanding of the illness/situation to assess misconceptions, aspects of news that will be surprising, and their unique information needs.
Determine if the patient or any family members are "numbers people" so they can be provided the type of information with which they feel most comfortable.
Schedule a future meeting to discuss the bad news and options (e.g., in an hour, the next day, the next week).
Source: [159; 160; 161] *Table 2*

Organizational Barriers

Barriers to end-of-life conversations also originate within the healthcare system. First, end-of-life discussions are not always considered part of routine care; clinicians are not always given the time and structure for discussing end-of-life issues. Next, coordination of these conversations, which becomes more necessary as the patient's illness progresses, may not be included as part of routine care. When patient care is provided by multiple clinicians across multiple sites, there is no clear directive about which clinician should be responsible for initiating and documenting end-of-life conversations. Last, decreased contact time and fewer long-term patient/clinician relationships inhibit end-of-life discussions [57].

No single clinician can successfully undertake all aspects of this challenge. End-of-life planning should be one component of a series of ongoing conversations that together can assist patients with advanced illness to approach death in accord with their own values and wishes. These necessary discussions can draw on the expertise of several disciplines, and the creation of a new professional role specializing in this area might be considered [57].

MENTAL HEALTH INTERVENTIONS FOR END-OF-LIFE CARE

Shortly after Kübler-Ross began to publish her work, group psychotherapists began developing systematic interventions for patients who were dying. This included Irvin Yalom in the 1980s, who was heavily influenced by existential philosophy. Yalom's work formed the basis for what became supportive expressive group psychotherapy (SEGT). SEGT was originally developed to help patients with metastatic breast cancer face and adjust to their existential concerns (e.g., death, meaninglessness), express and manage disease-related emotions, and enhance relationships with family and healthcare providers. SEGT challenged the thinking that group therapy for patients with terminal illness would be demoralizing [47; 59]. Over the next several decades, research in end-of-life care, patients' end-of-life needs, and the role of mental health professionals in these settings increased [47].

In the late 20th century, physician-assisted death (also referred to as medical aid in dying, physician aid in dying, physician-assisted suicide, or euthanasia) became a topic of interest as researchers sought to understand why some patients with life-limiting illness might want to hasten death [47]. Pain, depression, and physical symptoms were at first thought to be the primary motives behind the desire to hasten death, but literature in the 1990s and 2000s emphasized the psychological and existential correlates (i.e., depression, hopelessness, spiritual well-being) of physician-assisted death. This shift in emphasis led to the development of a number of psychotherapeutic interventions that focused on the psychological and spiritual needs of patients [47].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Institute for Clinical Systems Improvement, short-term psychotherapy modalities (e.g., dignity therapy) can provide reduction in depression and anxiety symptoms at the end of life.

(https://www.icsi.org/wp-content/uploads/2020/01/PalliativeCare_6th-Ed_2020_v2.pdf. Last accessed April 24, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

DIGNITY MODEL/DIGNITY THERAPY

Dignity therapy was one of the first interventions developed for use in end-of-life care [60]. This modality aims to relieve psycho-emotional and existential distress to improve the experiences of patients with life-limiting illness. It offers patients the opportunity to reflect on what is important to them and on what they might want to communicate to loved ones [61]. In dignity therapy, patients are invited to reflect on and later discuss what aspects of their life they most want recorded and remembered—often referred to as their "legacy" [62]. The sessions are audiotaped and guided by a framework of questions (provided in advance) that facilitate disclosure of the patient's thoughts, feelings, and memories. The interview is then transcribed and printed for the patient's review and editing, as desired. Once finalized, the document is given to the patient, who may (or may not) share with friends and family, as desired. In addition to providing a tangible legacy for the patient, dignity therapy helps enhance the patient's sense of meaning and purpose, thus contributing to a preservation of the patient's dignity [47].

A 2011 study revealed that the items most commonly included in legacy documents were autobiographical information, lessons learned in life, defining roles (e.g., vocations, hobbies), accomplishments, character traits, unfinished business, overcoming challenges, and guidance for others [63]. Dignity therapy has been shown to positively affect patients' sense of generativity, meaning, and acceptance near the end of life. Positive impacts on families and caregivers of dignity therapy participants provide additional support for the clinical utility of this intervention [64]. However, dignity therapy is not for every patient with terminal illness. Despite the demonstrated beneficial effects, its ability to mitigate outright distress (e.g., depression, desire for death or suicidality) has yet to be proven [65]. Acknowledged limitations of dignity therapy include having adequate time, space, and means to engage in this intervention. Dignity therapy also cannot be used with patients who are nonverbal or unconscious or with those who have severe cognitive limitations [66]. Further studies are needed to determine whether patients with specific types of terminal illnesses (e.g., oncologic, cardiac, renal, pulmonary, neurologic) or in specific age cohorts (e.g., pediatric, adult, geriatric) benefit more or less significantly in certain domains (e.g., measures of spiritual distress, autonomy, death anxiety) [66].

Life Review

Dignity therapy incorporates the concept of life review, which is the systematic and structured process of recalling past events and memories in an effort to find meaning and achieve resolution of one's life. It is conducted over four sessions in which patients chronologically review their childhood, adolescence, adulthood, and present situation. A health or mental health professional takes notes, but no other end product is produced [67]. Life review can be useful for patients of any age at the end of life [68]. Life review is typically structured around life themes (e.g., being a parent/grandparent, first job, life's work, important turning points) [69]. The process can be either reminiscent or evaluative. It also can teach or inform others and pass on knowledge and experience to a new generation. Life review conducted for therapeutic purposes can help patients cope with loss, guilt, conflict, or defeat and find meaning in their accomplishments [69]. In Western culture, life review may subsequently be shared with family or friends. For patients of other cultures, life review may be more communal and may involve rituals that are an important part of the dying process [34]. Few studies have evaluated therapeutic life review interventions, but preliminary results are promising [67].

Narrative Approach

Narrative practice is built on the assumption that people live multistoried lives. This perspective allows patients to shift from one life story to another to give meaning to their lives and shape their identities. A narrative approach frees the care team from the role of "expert" to the role of "helper" who facilitates patients' creation of personal stories of agency at times of life-limiting illness [70]. Narrative therapy is a practical psychotherapeutic process in which the professional and patient collaborate to deconstruct cultural and personal narratives that negatively affect the patient's sense of resources, efficacy, and identity. Together, clinician and patient discover and enrich positive, empowering, and helpful stories that originate in the patient's previous experiences [71]. Narrative therapy is patient-centered and goal-directed. Goals are to help patients improve their sense of self, separate problematic experiences away from their identity, and see themselves outside problems they may be facing. Narrative interventions can help patients and their families create new meaning of the patient's illness and end-of-life experiences [72].

TERROR MANAGEMENT THEORY

The concept of terror management theory was developed in 1986 and was based upon the work of Ernest Becker, a cultural anthropologist who had written about death and anxiety [73; 74]. Terror management theory is the concept that people feel threatened by a deep and terrifying fear of living an insignificant life that is destined to be erased by death. People cope with the awareness of their mortality in different ways. Some will adopt a worldview that allows them to find meaning, purpose, and enduring significance; others simply avoid thinking about death altogether and instead devote themselves to leaving behind a legacy that will make them "immortal" [74; 75]. While the fear of death can promote insecurity and bias or prejudice (based upon one's worldview), terror management theory helps people use their awareness of death to consciously choose to take positive steps to find meaning in their lives [74]. The awareness of mortality can motivate people to prioritize growth-oriented goals, live according to positive standards and beliefs, and foster the development of peaceful, charitable communities [76].

COGNITIVE-BEHAVIORAL THERAPY

The focus of traditional cognitive-behavioral therapy (CBT) is changing maladaptive thought patterns or perceptions that lead to mood disorders, such as anxiety and depression. But changing maladaptive thoughts to more realistic or positive ones does not always meet the needs of patients with life-limiting illness. These patients have very real fears about suffering and uncontrolled pain and other noxious symptoms, and their fears and thoughts are neither maladaptive nor unreasonable [77]. CBT adapted to end-of-life care can help patients identify "all-or-nothing" thinking and help them recognize that core parts of themselves remain unchanged [78].

Studies demonstrate that palliative care professionals have effectively applied CBT techniques to reduce mild-to-moderate anxiety or depression at the end of life and increase the patient's focus on the quality of remaining life [77; 79; 80]. For example, researchers incorporated elements of acceptance and commitment therapy (ACT) and dialectical behavior therapy (DBT). With ACT, patients learn to stop avoiding, denying, and struggling with their emotions. They instead learn to accept their emotions (and the source), accept their private circumstances, and not allow the circumstances to prevent them from moving forward in ways that serve their chosen values [81; 82]. DBT includes a strong educational component designed to provide patients with the skills to manage intense emotions [83].

MEANING-CENTERED PSYCHOTHERAPY

Meaning-centered group psychotherapy, based on the works of Viktor Frankl, was originally conceived as a group-based intervention for individuals with advanced cancer. Frankl's theory is existential in nature and postulates that the creation of meaning is a primary force of human motivation, even during times of great suffering [69]. The group therapy helps patients identify sources of meaning as a resource to sustain meaning, spiritual well-being, and purpose in the midst of suffering [47; 69]. Meaning-centered psychotherapy was later adapted for use with individual patients [84]. The goals of meaning-centered psychotherapy are to provide support for patients to explore personal issues and feelings related to their illness; to help patients identify sources of meaning; and to help patients discover and maintain a sense of meaning in life, even as their illness progresses [47]. Randomized controlled trials conducted to date, totaling nearly 800 patients, have demonstrated support for meaning-centered psychotherapy in improving spiritual well-being and reducing psychological stress in patients at the end of life [85; 86; 87]. The extent to which the observed results can be attributed to the patient's changes in sense of meaning require further study [47]. Like dignity therapy, meaning-centered psychotherapy has fueled multiple adaptations to target unique clinical populations and settings (e.g., bereaved family members, caregivers) [88; 89; 90].

COMPASSION-BASED THERAPY

Compassion-based therapy is rooted in an evolutionary analysis of basic social and emotional systems that motivate humans to live in groups, form hierarchies, help and share through alliances, care for kin, respond to threats, and seek states of contentment/safeness [91]. Compassion-based therapy can be supportive to those facing end-of-life decision making. It is inextricably linked to the inherent values, needs, and expectations of patients, families, and healthcare providers. Compassion coupled with a collaborative framework sustains patient- and family-centered care in end-of-life practice settings [92].

Compassion-based therapy offers a novel, transdiagnostic approach for reducing psychopathology and increasing well-being. It changes the focus of therapy from individual thoughts or unconscious conflicts toward the development of affiliative and prosocial functioning [93]. One overview of compassion-based therapies found at least eight different interventions (e.g., compassion-focused therapy, mindful self-compassion, cognitively based compassion training), six of which have been evaluated in randomized controlled trials. Compassion-based interventions demonstrated reduced suffering and improved life satisfaction for patients [93]. A systematic review conducted to assess the effectiveness of compassion-based therapy analyzed 14 studies, including three randomized controlled studies [94]. Compassion-focused therapy was effective with depressive disorders and for people who are highly self-critical. Compassion-based therapy is most effective when used in conjunction with other types of treatment and therapy [94].

Being Present

One of the most important therapeutic and compassionate aspects a health professional can offer is their presence. Listening to and allowing patients to express their end-of-life experience is healing and can be more comforting than guidance. One study investigated how palliative care chaplains work with patients at the point when it has been decided to cease active treatment, the point at which patients risk losing hope and falling into despair [95]. The author identified four types of presence in the chaplain-patient relationship that were a result of the chaplain's "being with the patient." Each type of presence (i.e., evocative, accompanying, comforting, hopeful) represented a discernable development in the chaplain/patient relationship—a theory of chaplain as hopeful presence [95].

The effects of educating patients and families about the importance of being present was the goal of a descriptive study that included 19 critical care nurses [96]. The nurses were interviewed to understand their experiences and perceptions about caring for patients and families transitioning from aggressive life-saving care to palliative and end-of-life care [96]. The nurses prioritized educating the family, advocating for the patient, encouraging and supporting the family's presence, protecting families, and helping them create positive memories. The family's presence at the end of life also helped them to process the reality of their loved one's death and make peace with it [96].

OTHER INTERVENTIONS

Researchers and clinicians have developed a variety of other interventions for end-of-life care. One proposed treatment is called short-term life review (STLR). Like dignity therapy, STLR interviews the patient for the purpose of creating a legacy album, but STLR differs from dignity therapy in the substance of the interview. A single published randomized controlled trial has examined the utility of STLR, and little research has been conducted to support the STLR approach. The research that has been published has suggested increases in spiritual well-being, sense of hope, and death preparedness among patients with terminal cancer [47; 97; 98].

Managing cancer and living meaningfully (CALM) is a brief, structured intervention developed for patients with advanced and/or terminal cancer [47; 99; 100]. The focus of CALM is similar to meaning-centered psychotherapy, but it provides less emphasis on spiritual well-being and existential issues due to its longer timeframe [47]. The first large-scale randomized controlled trial of CALM reports that individuals demonstrated significantly greater improvements in depressive symptoms and overall quality of life compared to those who received usual care [101].

Mindfulness

Mindfulness is the practice of paying deliberate attention to experiences of the present moment with openness, curiosity, and a willingness to allow things to be as they are [102]. End-of-life care is, by its nature, rooted in mindfulness through [103]:

- The healthcare team providing steady presence and compassion to the dying patient
- Bringing one's full attention to clinical assessments and supportive interactions and acknowledging what arises during these interactions for patients, families, and clinicians
- Being attuned to the dying and their needs, remaining present with their suffering
- Being genuinely interested in the patient's/family's experiences
- Allowing the full expression of personal experiences, with no attempt to change or fix them
- Cultivating compassion and acknowledging our shared humanity

Spiritual Care

Spiritual care is considered a basic tenet of palliative care and a responsibility of the entire end-of-life care team. Patients who receive good spiritual care report greater quality of life, better coping, and greater well-being, hope, optimism, and reduction of despair at the end of life. Despite these benefits, patients and caregivers often refuse spiritual care when offered. One study that sought to understand this reluctance focused on the effect of education. The authors reported that an educational intervention, which included explaining the services of hospice chaplains and the evidence-based benefits of spiritual support, led to greater patient/caregiver acceptance of spiritual care [104]. End-of-life counselors, therapists, and social workers are uniquely positioned to work with patients to explore the variables that they and their families use as guiding principles when making difficult decisions [105]. This requires assessing the patient's spiritual, religious, and existential needs (i.e., spiritual needs) to provide appropriate interventions [106].

The specifics of how to conduct assessment are determined by individual healthcare organizations but usually consist first of obtaining a spiritual history of the patient and the patient's family. A variety of tools are available. The FICA acronym asks four questions about faith, importance/influence of beliefs, community involvement, and addressing issues of care [107]. The HOPE questions inquire about patients' sources of hope and meaning, whether they belong to an organized religion, their personal spirituality and practices, and what effect their spirituality may have on end-of-life care [108]. Reported barriers to spiritual assessment include clinician lack of time/experience, difficulty identifying patients who wish to discuss spiritual beliefs, and addressing concerns not regarded as the clinician's responsibility. Assessing and integrating patient spirituality into end-of-life care can build trust and rapport and strengthen the patient's relationship with the end-of-life care team [108]. Unaddressed spiritual issues may frustrate attempts to treat other symptoms and adversely impact the patient's quality of life [105].

Art and Music Therapy

Art and music therapists are becoming increasingly available to palliative care teams and are advancing the diverse and unique clinical services available to effectively meet the holistic needs of patients with serious illness [109]. Art can connect with deep psychological and physical pain, allowing the patient to find expression and relief. Studies have found that expressive arts (e.g., paint, clay, textiles, drawing) help patients more effectively deal with ambivalent emotions regarding life-death issues and communicate with their families about their feelings. It helps patients articulate their end-of-life journey beyond language [110; 111].

Art therapy also may be helpful in reducing burnout among end-of-life care providers by enhancing their emotional awareness, fostering meaning-making, and promoting reflection on death. One study found significant reductions in exhaustion and death anxiety in end-of-life care providers who participated in an art therapy program [38].

Music therapy incorporates music chosen by the patient in consultation with a qualified music therapist. The music is often chosen to arouse specific emotions that allow the patient to more easily access, recall, and interrogate memories, with the goal of understanding the role those memories play in the patient's current circumstances [38]. Music therapy also may be an effective adjuvant to pain management therapy [38].

BEREAVEMENT

As stated, Kübler-Ross wrote that it could be helpful if people could talk about death and dying as an intrinsic part of life and emphasized the importance of listening as a way for practitioners to support terminally ill patients and their families when confronting the realities of impending death [46; 47]. She subsequently applied her model to the experience of loss in many contexts, including grief and other significant life changes [112]. This model identified five stages of bereavement—denial, anger, bargaining, depression, and acceptance. Though the stages are frequently interpreted strictly and hierarchically, this was not Kübler-Ross's intention. She expressed that individual patients could manifest each stage differently, if at all, and might move between stages in a nonlinear manner [112]. Her model has received criticism in recent years and many alternative models (some based on Kübler-Ross's model) have been developed [112; 113; 114; 115].

PROLONGED GRIEF DISORDER

What are the criteria for the diagnosis of prolonged grief disorder?

The death of a loved one is followed by an intensely emotional and disruptive period that gradually attenuates as the death is comprehended and accepted and its consequences understood (integration). It is a highly stressful period accompanied by the need to attend to a range of things not usually on one's agenda. Most people meet the coping demands and are able to find a pathway through the sorrow, numbness, and even guilt and anger that are part of the normal grieving process. A small minority, however, do not cope effectively. For them, the feelings of loss become debilitating. They do not improve with the passing of time and can become so long-lasting and severe that recovering from the loss and resuming a normal life is impossible without assistance [116]. These people are suffering from prolonged grief disorder, a syndrome in which healing is impeded and acute grief is intense and prolonged.

It is important to differentiate grief from depression. Grieving can be an appropriate response to loss, but if the symptoms persist, the Institute for Clinical Systems Improvement recommends that depression be considered.

(https://www.icsi.org/wp-content/uploads/2020/01/PalliativeCare_6th-Ed_2020_v2.pdf. Last accessed April 24, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

Prolonged grief disorder is the newest disorder to be added to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). The disorder was added to the DSM-5-TR in 2022 after several decades of studies that suggested "many people were experiencing persistent difficulties associated with bereavement that exceeded expected social, cultural, or religious expectations" [117]. Prolonged grief disorder often co-occurs with other mental disorders (e.g., PTSD, anxiety, depression). Sleep problems, such as poor long-term sleep, occur in an estimated 80% of people with this disorder [118].

Prolonged grief disorder is defined as "intense yearning or longing for the deceased (often with intense sorrow and emotional pain) and preoccupation with thoughts or memories of the deceased. In children and adolescents, this preoccupation may focus on the circumstances of the death" [117]. In adults, this intense grief must still be present one year after a loss to be considered prolonged grief disorder; in children, the timeframe is six months. Additionally, the individual with prolonged grief disorder may experience significant distress or problems performing daily activities at home, work, or other important areas [117]. It is important for clinicians to differentiate prolonged grief disorder from usual acute grief, as well as depression and anxiety disorders [116]. Risk factors for prolonged grief disorder include past losses, separations that can impact current losses, and a history of depressive illness [115]. Symptoms include [117]:

- Identity disruption (e.g., feeling as though part of oneself has died)
- A marked sense of disbelief about the death
- Avoidance of reminders that the person is dead
- Intense emotional pain (e.g., anger, bitterness, sorrow)
- Difficulty reintegrating (e.g., unable to engage with friends, pursue interests, plan for the future)
- Emotional numbness
- Feeling that life is meaningless
- Intense loneliness and feeling of being detached from others

An estimated 7% to 10% of bereaved adults will experience the persistent symptoms of prolonged grief disorder, and 5% to 10% of bereaved children and adolescents will experience depression, PTSD, and/or prolonged grief disorder [118; 119]. Treatments using elements of CBT have been found to be effective in reducing symptoms [117]. Complicated grief treatment incorporates components of CBT and other approaches to help patients adapt to the loss. It focuses on accepting the reality of the loss and on working toward goals and a sense of satisfaction in a world without the loved one [118]. Research has shown that CBT is effective in addressing sleep problems associated with prolonged grief disorder. CBT also has been

shown to be superior in long-term effects to supportive counseling in children and adolescents experiencing symptoms of prolonged grief disorder [119; 120].

Bereavement support groups can provide a useful source of social connection and support. They can help people feel less alone, thus helping to avoid the isolation that could increase the risk for prolonged grief disorder. Despite the existence of effective treatments, people experiencing prolonged grief disorder may not seek help. One study of 86 bereaved caregivers with symptoms of prolonged grief disorder found that only 43% accessed mental health services [121].

PRACTICAL, ETHICAL, AND LEGAL CONSIDERATIONS

Planning ahead provides patients with the most control over their end-of-life care, but not all patients have the opportunity to do so. End-of-life planning for the patient will include knowing the type of care they need and want, knowing where they want to receive this care, knowing what documents (e.g., advance directives) and associated costs to include in planning, and determining who will help carry out their wishes [122].

CAREGIVING AND SURROGACY

The vast majority (80%) of care given to hospice patients is provided by informal and unpaid caregivers who are often family members. They can be responsible for everything from the management of household and finances to medical and personal care. Providing this level of care can contribute to increased stress and health problems [123]. Caregivers often report significant levels of anxiety, depression, and perceived stress as well as poorer physical health and decreased quality of life compared with non-caregivers [124]. In one study, nearly one-third (31%) of caregivers reported moderate-to-high levels of anxiety [125]. Even family members who are not caregivers experience distress and require support. Supporting the growing number of family and other unpaid caregivers is an urgent public health issue. The need for adequate support is especially pressing when older patients and the loved ones who assist them are most vulnerable, as at the end of life [126]. Health and mental health professionals can help the caregiver and/or family by preparing them for their loved one's death, treating symptoms of burnout and stress, and offering grief counseling when desired [127].

Family members may be called upon to make decisions on their loved one's behalf if incapacitation becomes an issue. Ideally, the decision-making process will reflect the patient's physiologic realities, preferences, and recognition of what, clinically, may or may not be accomplished [128; 129]. Being a surrogate decision maker is stressful for many and can have negative emotional effects that last months or years [130]. Frequent tension can occur between the desire to respect the patient's values and the fear of responsibility for a loved one's death, a desire to pursue any chance of recovery, and a need to ensure family well-being [131]. Counseling for the surrogate both during and after the decision-making process can be beneficial.

Shared decision making also has been found to be beneficial. Healthcare providers can encourage decision makers to involve other family members. They can repeat relevant information in simple language, prompt them to think about what the patient would or would not want, and frequently remind them that everything that can be done is being done [132]. Support for the surrogate should foster respect for patient preferences and values and help reduce guilt about decisions made following the patient's death [132]. An ideal surrogate will participate in collaborative decision-making with care providers. If a surrogate avoids communication or requests interventions that are clearly not considered in the patient's best interest, counseling should be provided. If counseling is unsuccessful, replacement of the surrogate should be considered [133]. Family members who reside far away and who are not designated as decision maker also can create difficulties by trying to undo, contest, undermine, or alter decisions made by local family members who have long been involved in the patient's care. These disagreements can compromise the ability of the patient's healthcare team to provide quality care. These limits of formal advance care planning have led some practitioners to assert that informal conversations with patients' significant others are most critical to end-of-life planning [134].

Current practice frequently fails to promote patient goals. This is an area for future research and improvement. In the meantime, clinicians should encourage patients to document their own goals, including treatment preferences and preferences regarding how they want decisions to be made for them during periods of decisional incapacity. This is achieved through advance care planning [135; 136].

ADVANCE CARE PLANNING

Advance care planning is widely considered an essential step toward achieving end-of-life care that is consistent with the preferences of dying patients and their families. Advance care planning typically includes a living will and a durable power of attorney for health care, which enable patients to articulate and convey their treatment preferences while they are cognitively intact [136]. Advance care planning documents also can include do not resuscitate (DNR) orders, medical/physician order for life-sustaining treatment (MOLST/POLST), and informal documents of preference or other healthcare proxies. Ideally, these documents reflect discussions among the patient's family, surrogate, and healthcare provider about the patient's preferences for health care in the context of serious illness [129]. Advance care planning is considered an essential step for achieving a "good death" in which physical pain and emotional distress are minimized and the patient's and family members' treatment preferences are respected [134]. Advance care planning is associated with greater use of palliative care

among dying patients, lower medical expenditures at the end of life, and less distress among patients and patients' families.

Race and socioeconomic disparities in rates of advance care planning have been documented. Policy advances (e.g., Medicare reimbursement for doctor-patient consultations) may increase rates of planning among populations who may not have access to professionals who encourage such preparations [136]. Health and mental health professionals can assist families in the process of preparing advanced care planning documents. Being a mediator in advance care planning conversations can provide clarity for patients and family members about the patient's wishes regarding death [137].

ETHICAL/LEGAL ISSUES

Ethical concerns and legal considerations can influence counseling at the end of life. Health and mental health providers are on the frontline supporting and guiding the patient and the patient's family through the dying process.

Autonomy

Autonomy, as viewed from the perspective of patients at the end of life, includes two core domains: "being normal" and "taking charge" [138]. These two domains account for the circumstances and clinical realities of people with life-limiting illness and allow clinicians to better understand their needs. Autonomy is, however, not just a concern when making choices of treatment for end-of-life care but also when supporting patients in their daily lives and active preparations for dying. This support can help relieve the patient of stress and the fear of being a burden to family [138]. When a patient expresses a fear over the loss of autonomy, it is important for clinicians to determine the source of the fear. Common sources of such fear include fear of becoming physically dependent on life-supporting technology; fear of losing independence; and fear of loss of engagement in meaningful activity. Often, the patient is simply expressing a desire to preserve self-determination regarding end-of-life care and planning [45]. The healthcare team respects patients' autonomy by giving them the information needed to understand the risks and benefits of a proposed intervention, as well as the reasonable alternatives (including no intervention), so that they may make independent decisions [139].

Distributive Justice

Distributive justice is the fair, equitable, and appropriate distribution of healthcare resources. It requires impartiality in the delivery of health service. Issues of distributive justice encountered in healthcare settings include the allotment of scarce resources, care of uninsured patients, conflicts of interest based on religious or legal grounds, and public health and safety issues. Despite these constraining influences, healthcare providers have an ethical obligation to advocate for fair and appropriate treatment of patients at the end of life [140; 141].

Beneficence

The principle of beneficence is the obligation of health and mental health professionals to act in the best interest of the patient [137]. Beneficence also includes preventing and avoiding harm and defending the most useful intervention for the patient [140; 141]. Beneficence is fundamental to dilemmas about the discontinuation, withholding, or withdrawal of medical treatment [137]. When wishes about end-of-life care are not known or cannot be communicated by the patient, end-of-life decisions should be made by the healthcare team as a result of consultations with the family or healthcare proxy [137].

Nonmaleficence

Nonmaleficence is the principle of refraining from causing unnecessary harm (i.e., first, do no harm) [137]. It also refers to the moral justification behind an intervention that might cause some pain or harm; harm is justified if the benefit of the intervention is greater than the harm to the patient and the intervention is not intended to harm [137]. The emphasis in nonmaleficence is on relieving the symptoms that harm the patient [142]. Health and mental health providers can exercise nonmaleficence by having an understanding of the moral principles and ethical codes governing end-of-life care. They can prevent undue harm by being as knowledgeable as possible about impending illnesses through relationships with the interprofessional team [137].

CULTURALLY COMPETENT CARE AT THE END OF LIFE

What is the role of interpreters at the end of life?

The clinician/patient discussion about end-of-life care is often a challenge and one that can be further complicated when the patient's cultural norms differ from that of the clinician. As discussed, values of medical care emphasize autonomy and individual rights to make life choices [143]. The Patient Self Determination Act of 1990 ensured that those rights are protected. This includes the rights to treatment choices, informed consent, truth-telling, open communication with healthcare providers, and control over the individual's own life and death [143; 144]. However, these core values may be in conflict with the values of many ethnic and culturally diverse groups in the United States and may lead to health disparities, fragmented care, inadequate or inappropriate symptom management, miscommunication with the patient and family, and a difficult and poor death for the patient [143].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Institute for Clinical Systems Improvement asserts that clinicians caring for patients with serious illness should examine their own cultural values and assumptions about what constitutes "good" care for patients nearing the end of life, recognizing not all patients will share these same values, and ensure goals and decisions remain centered around the patient's values/beliefs.

(https://www.icsi.org/wp-content/uploads/2020/01/PalliativeCare_6th-Ed_2020_v2.pdf. Last accessed April 24, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

Enhanced cultural competency in end-of-life issues continues to be identified as a need for clinicians who provide care for patients at the end of life [143]. Healthcare providers should understand and recognize the specific influences that culture has on a patient's behavior, attitudes, preferences, and decisions about end-of-life care. It is important to note that a patient's identification as a member of a particular ethnic group or religion does not necessarily mean that the patient or patient's family adheres to beliefs associated with that ethnicity or religion [143]. Other factors (e.g., age, race, sex, ethnicity, health status, religion) also can influence how patients approach the end of life, and their cultural and religious backgrounds influence their definitions of and perceptions about what constitutes quality of life, suffering, and pain [145].

Other areas of end-of-life care that vary culturally include the method used for communicating "bad news," the locus of decision making, and attitudes toward advance directives and end-of-life care specifics [146]. In contrast to the emphasis on "truth telling" in the United States, it is not uncommon for healthcare professionals outside the United States to conceal serious diagnoses from patients, because disclosure of serious illness may be viewed as disrespectful, impolite, or even harmful to the patient. The emphasis on patient autonomy may conflict with the patient's preferences for family-based, physician-based, or shared family-physician-based decision making. Lower rates of completion of advance directives by patients of some ethnic backgrounds suggests a distrust of the healthcare system, healthcare disparities, and underutilization of health care [146; 147; 148].

An assessment should be made of how acculturated a patient and family are, their language skills, and whether an interpreter is needed [143]. The clinician should assess for [149]:

- Openness/willingness of the patient/family to discussing/accepting the diagnosis, prognosis, and death
- How decisions are made and what influences decision making (e.g., age, gender, hierarchy, quality of interfamily communication)
- What does physical pain mean and how should it be managed?
- Is there spiritual pain? Does the patient desire the help of a spiritual advisor? Does the patient/family want time and space for praying, meditation, and other rituals?
- The relevance of religious beliefs regarding the meaning of death
- How the body should be handled following death

The clinician also can take advantage of available resources, including community or religious leaders, family members, and language translators [149]. It is important to note that using professional interpreters for patients and with limited English proficiency will help ensure quality care. Convenience and cost lead many clinicians to use "ad hoc" interpreters (e.g., family members, friends, bilingual staff members) instead of professional interpreters. However, professional interpreters are preferred for several reasons. Several states have laws about who can interpret medical information for a patient, so healthcare professionals should check with their state's health officials about the use of ad hoc interpreters [150]. Even when allowed by law, the use of a patient's family member or friend as an interpreter should be avoided, as the patient may not be as forthcoming with information and the family member or friend may not remain objective [150]. Children should especially be avoided as interpreters, as their understanding of medical language is limited, and they may filter information to protect their parents or other adult family members [150]. Individuals with limited English language skills have actually indicated a preference for professional interpreters rather than family members [151].

Also important is the fact that clinical consequences are more likely with ad hoc interpreters than with professional interpreters [152]. A systematic review of the literature showed that the use of professional interpreters facilitates a broader understanding and leads to better clinical care than the use of ad hoc interpreters, and many studies have demonstrated that the lack of an interpreter for patients with limited English proficiency compromises the quality of care. The use of professional interpreters improves communication (errors and comprehension), utilization, clinical outcomes, and patient satisfaction with care [151; 153]. One review of case studies regarding professional interpretation noted that "patients with limited English proficiency in the United States have a legal right to access language services, and clinicians have legal and ethical responsibilities to communicate through qualified interpreters when caring for these patients" [154].

Culturally competent counseling for patients at the end of life begins with understanding their differing cultural, religious, and other important influential factors. It involves listening to and learning about patients' varying attitudes, preferences, and practices in order to integrate them into an appropriate plan of care [155]. Clinicians should treat all patients with dignity, respecting their rich cultural traditions and incorporating them into the plan of care. It means communicating with the patient and the patient's family in advance about how the plan of care is aligned with their beliefs, concerns, values, and preferences [145]. To deny the expression of different cultural worldviews in the context of end-of-life care would be to rob patients of the security and serenity that their cultural beliefs give them when faced with uncertainty and fear [156].

CONCLUSION

Health and mental health professionals provide services to diverse individuals in a variety of settings, including end-of-life settings, as part of an interprofessional team. In the end-of-life setting, these professionals help dying patients and their families prepare for death with education and supportive therapeutic interventions that address the patient's physical, emotional, social, spiritual, and practical needs using a patient-centered, culturally sensitive approach [10; 157]. Clinicians can regularly promote communication and education about end-of-life care issues by taking the initiative and discussing each patient's goals for end-of-life care [55]. The better informed the patient and family are, the more likely their decisions about end-of-life care will reflect their beliefs, values, and the best interests of the patient. This means having difficult conversations. All professionals should work to become comfortable with the most uncomfortable of topics. This work is not done alone. It is essential to lean on and consult colleagues and other members of the care team. End-of-life care often involves interactions between caregivers and various professionals (e.g., physicians, nurses, social workers, mental health professionals, clergy) who have distinct roles in preparing caregivers for the patient's death [158]. Aligning on key concepts and approaches to care can help to ensure that the best possible care and support are given at the end of life.

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

Pressure Injuries and Skin Care

Audience
This course is designed for nurses in all practice settings, particularly those caring for patients at high risk for developing pressure injuries.

Course Objective
The purpose of this course is to provide nurses with the information necessary to accurately identify, treat, and manage skin breakdown (pressure injury), thereby improving patient outcomes and quality of life.

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

1. List the key structures and functions of the skin.
2. Describe skin changes throughout the life span.
3. Identify causative factors contributing to pressure injury occurrence.
4. Accurately identify each stage of pressure injury development.
5. Identify risk factors leading to the development of pressure injuries.
6. Outline characteristics of a validated and reliable pressure injury risk assessment tool.
7. Complete thorough skin and pain assessments.
8. Outline an individualized program of skin care, including nutritional support, documentation, and patient education.

Faculty
Maryam Mamou, BSN, RN, CRRN, CWOCN, is an Irish-trained RN who has lived and worked in the United States for 20 years. During her career, she has completed a BSN and went on to become a certified rehabilitation nurse, a certified life care planner, and more recently a certified wound ostomy and continence nurse. She is a graduate of the wound ostomy and continence program at Emory University in Atlanta, Georgia, and is nationally certified in these areas.

Ms. Mamou has worked in various rehabilitation settings and has first-hand experience of how pressure ulcers impact patients' recovery and quality of life. She has held positions as staff nurse, unit coordinator, educator, and director of nursing in home health care. She has been involved in developing and implementing several staff education programs in a variety of settings. She was most recently employed as a wound ostomy and continence nurse at East Alabama Medical Center in Opelika, Alabama.

Faculty Disclosure
Contributing faculty, Maryam Mamou, BSN, RN, CRRN, CWOCN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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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

A complete skin assessment and accurate documentation of the assessment findings are critical elements of the nurse's role in providing care for patients with pressure injuries. In order to perform a thorough assessment, nurses should have a working knowledge of the general characteristics of the skin, its functions, and the changes that occur in the skin throughout an individual's life span.

Each patient deemed at risk for skin breakdown or with evidence of breakdown should have an individualized program of skin care, including nutritional support and patient and family education, among other elements. Ongoing evaluation and documentation of the skincare program and whether it is meeting its goals is necessary.

GENERAL CHARACTERISTICS OF SKIN

Skin is the largest organ in the body. In the average person it covers approximately 3,000 square inches [1]. In total, it weighs around six pounds, or up to 15% of the total adult body weight. Intact skin is dry, supple, and has a pH ranging from 4 to 6. It varies in thickness from 0.5 mm in the tympanic membrane to 6 mm on the soles of the feet and the palms of the hands. Frequent bathing and episodes of incontinence remove naturally occurring oils from the skin [2]. However, as an organ, the skin is able to withstand limited mechanical and chemical assaults.

SKIN STRUCTURES

What are the two primary layers of the skin?

Human skin has two primary layers: the epidermis (outer layer) and the dermis (inner layer). The basement membrane separates the two layers. Beneath the dermis is the hypodermis, which is a layer of connective tissue also referred to as the subcutaneous tissue.

Epidermis

The epidermis is a thin layer that regenerates itself every four to six weeks. It contains no blood vessels and receives its blood supply from the inner (dermis) layer. Nerve fibers are located throughout the epidermis. It is divided into five layers—presented in order from the outermost layer inward: stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale.

The stratum corneum is composed of dead keratinized cells and is constantly being sloughed off and renewed from below [2]. It has an acid mantle, an oily layer with reduced pH, provided by sebum, the substance secreted by the sebaceous glands onto the skin surface via the hair follicles.

The stratum lucidum, also known as the clear layer, is found in areas where the epidermis is thicker, like the palms of the hands and the soles of the feet [1]. It lies directly below the stratum corneum. The next layer, the stratum granulosum, is composed of one to five layers. It is believed to help with keratin formation.

The stratum spinosum is referred to as the "prickly layer" because of the spine-like shape of the cells [2]. In this layer, skin cells begin to flatten as they are migrating toward the skin surface. The stratum basale, also known as the stratum germinativum, is the innermost layer of the epidermis. It is composed of a single layer of constantly dividing cells that form new cells. These new cells migrate to the stratum corneum [1]. Cellular migration usually takes 28 days, but this rate is affected by aging and chemotherapy.

Rete pegs and rete ridges are interlocking structures that extend down from the epidermis into the dermis. These finger-shaped downward projections on the epidermis interlock with upward projections from the dermis. Rete pegs and ridges ensure that all the skin layers move together.

The epidermis contains many specialized cells that affect patient health and appearance. The cells of the skin that provide immune protection (dendritic or Langerhans cells) are found in the stratum granulosum and the stratum spinosum. Melanocytes are found only in the epidermis and are responsible for differences in skin color. The number of melanocytes is approximately the same in normal skin regardless of skin color, but the amount of the pigment melanin produced varies from person to person and from one area of skin on the body to another.

Basement Membrane

The basement membrane's main function is to anchor the epidermis to the dermis. It contains several protein substances, including collagen, and is the layer that is affected in blister formation [1].

Dermis

The dermis is the most important part of the skin and is often referred to as the "true skin" [3]. It is the thickest layer of the skin, varying in thickness from 0.2 mm to 4 mm. The reticular dermis anchors the skin to the subcutaneous tissue and contains sweat glands, hair follicles, nerves, and blood vessels [1]. The dermis also contains the sebaceous glands, which secrete sebum, a substance rich in oil that lubricates the skin.

The major proteins found in the dermis are collagen and elastin [1]. Collagen gives skin its tensile strength, while elastin provides the skin with elastic recoil. This characteristic prevents the skin from being permanently reshaped. The dermis is divided into two areas: the papillary dermis, which contains capillaries for skin nourishment, and the reticular layer, which is comprised of thick collagen fibers. The dermis also contains Meissner and Vater-Pacini corpuscles, the receptors that sense pain and pressure.

Subcutaneous Tissue

Beneath the dermis lies subcutaneous tissue, which attaches the skin to the underlying structures. Subcutaneous tissue contains adipose tissue, connective tissue, blood vessels, lymphatics, and nerve endings. It is the adipose tissue that provides protection from pressure and shear. Elderly patients who may have inadequate subcutaneous tissue are at high risk for deep tissue injury due to pressure and shear [2].

Muscle and Fascia

Muscle and fascia are highly vascularized tissue that is most sensitive to ischemia. Pressure damage usually originates here [2]. The skin receives its blood supply from vessels that originate in the muscle tissue.

FUNCTIONS OF THE SKIN

The skin protects against mechanical and chemical trauma, pathogens, dehydration, and malignancy [2]. One of the most important functions of the skin is acting as a physical barrier to micro-organisms, protecting the body against infection. The acid mantle present in the epidermis also retards the growth of micro-organisms.

The skin immune system provides protection as well [1]. Macrophages found in the dermis are phagocytic cells that provide defense against pathogens for the skin and for open wounds. These macrophages also promote wound healing.

Mast cells are present in the skin and are the primary cells involved in allergic reactions. They also help protect against parasites.

The skin maintains heat regulation by the process of vasodilation and vasoconstriction, sweating and shivering [2]. Fluid evaporating from the skin allows for cooling to occur. The amount of sweat excreted can range from 100 mL to 2 liters in one hour [2]. As a result, the skin plays an important role in electrolyte balance and hydration.

Nerve endings in the skin provide information about the external environment and protection. Some areas of the skin are more sensitive than others (e.g., the fingertips are more sensitive than the back). Any loss of sensation increases the chances of injury.

The skin is also involved in the metabolism of certain vitamins. Specifically, the effect of ultraviolet B light on sterols in the skin causes synthesis of vitamin D. Certain drugs and some toxic substances (e.g., pesticides) can also be absorbed directly through the skin and into circulation.

Finally, skin provides for expression and body image [2]. Skin plays a vital role in self-esteem and social communication. Skin characteristics have an impact on how an individual communicates both verbally and nonverbally, and how the other person reacts to that individual. It also provides significant social cues regarding health and vitality.

SKIN THROUGHOUT THE LIFE SPAN

Fetal and Neonatal Skin

Fetal skin appears to have increased amounts of hyaluronic acid, which is associated with fetal scarless healing. Studies indicate that intrauterine surgery done late in the second trimester or early in the third trimester usually results in no scars [2].

Neonatal skin is more permeable due to the immature stratum corneum. During the first two weeks of life, topical administration can equal intravenous (IV) administration in terms of absorption [2]. Because infants have thinner skin and nails, epidermal stripping can occur easily.

Adult Skin

Adult skin shows a gradual increase in epidermal turnover time and decreasing dermal thickness. In young adults, epidermal turnover is around 21 days; by 35 years of age, this time doubles [2]. In addition, melanocytes decrease 6% to 8% each decade after 30 years of age. This loss of skin melanocytes is thought to increase the risk of skin cancer [1].

Elderly Skin

How does skin change in older adults?

In elderly individuals, there is a 50% reduction in the cell turnover rate in the stratum corneum (outer most layer) and a 20% reduction in dermal thickness. Elderly patients experience an overall reduction in dermal vascularization and associated drop in blood flow to the skin. The collagen bundles in the dermis shrink, causing permanent wrinkles to develop [2].

Rete ridges and pegs flatten, resulting in decreased adhesion between the skin layers. The area of contact between the epidermis and the dermis is reduced by 50% [4]. There is increased capillary fragility; slight pressure can cause bruising. A decrease in subcutaneous tissue causes a reduction in thermal insulation and increases the risk of shear/pressure injury. Reduced activity of sweat glands and sebaceous glands can lead to dry skin.

Elderly individuals experience a drop in the number of Langerhans cells, a 50% decrease in the number of mast cells, and up to a 50% decrease in the function of the remaining cells. As a result, there is an increased risk of skin cancer and fungal and other infections [1].

Other age-related changes include decreased absorption, reduction in the skin's ability to synthesize vitamin D, and significantly marked reduction in the ability of the skin to sense pressure, heat, and cold. Decreased cellular competence and activity leads to a reduction in cell repair and the increased possibility of nonhealing wounds [2].

PRESSURE INJURIES

Where do pressure injuries usually occur?

In 2016, the National Pressure Advisory Panel (NPUAP), now the National Pressure Injury Advisory Panel (NPIAP), released updated definitions for pressure ulcers and staging classification [5; 6]. In this revision, the term "pressure injury" replaced "pressure ulcer," to alleviate confusion between injury to intact skin and open ulcers. According to the NPIAP, a pressure injury is localized damage to skin and/or underlying soft tissue and usually occurs over a bony prominence. It is the result of prolonged pressure or pressure combined with shear and/or friction. A pressure injury can present as intact skin or an open ulcer. Patients at risk for pressure injury (e.g., immobile patients) are also at risk for friction and shear damage. The tolerance of soft tissue for pressure and shear also may be affected by microclimate, nutrition, perfusion, comorbidities, and condition of the soft tissue [6]. The term "pressure injury" will be used throughout the remainder of this course.

Pressure injuries usually occur over a bony prominence such as the sacrum, the ischial tuberosity, the trochanter, and the heels, but they can occur anywhere on the body. In some cases, pressure injuries will develop around a tracheostomy tube or under a cast, splint, or cervical collar [1]. The most common locations for pressure injuries are the sacrum and the heels because there is less soft tissue present between the bone and the skin in these areas. An estimated 95% of pressure injuries occur on the lower body; of these, about 65% develop in the pelvic area and 30% in the lower extremities [7]. There is a two to six times greater mortality risk with pressure injury development. Many factors impact the level and extent of tissue trauma (***Table 1***) [8].

PRESSURE AND SHEAR

Pressure that results in the development of injuries is defined as compression of soft tissues between two rigid surfaces. For example, blood vessels, muscle, subcutaneous fat, or skin may be compressed between a bone and an external surface, such as a bed or chair. The end result is ischemia and necrosis. All the tissues between the two points of pressure are affected, but the tissue closest to the bony prominence suffers the greatest damage. It is important to note that low-intensity pressure over a long period of time can create tissue damage, just as

FACTORS CONTRIBUTING TO THE FORMATION OF PRESSURE INJURIES
Extrinsic Factors
Undue, prolonged pressure
Shear
Friction
Moisture
Abnormal posture
Intrinsic Factors
Altered consciousness
Decreased or absent sensations
Nutritional factors (under- or over-nourished)
Anemia
Edema
Atherosclerosis
Aged-related changes
Acute illness
Sleep
Medications
Cardiovascular changes
Emotional stress
Source: [8] *Table 1*

high-intensity pressure over a short period of time can result in damage [2]. Application of high pressure for shorter duration not only causes tissue necrosis due to blockage of capillaries but also produces pressure effect on the larger vessels, causing thrombosis (usually venous). Hence, the deleterious effect of high pressure for short duration is much more than that of low pressure for a longer duration. This has been proven by the observation that when the high pressure is relieved, ischemia persists due to effects on the adjacent larger vessels; upon relief of low pressure, the normal hyperemic response compensates for the temporary ischemia and the tissue does not undergo degeneration [8].

Pressure injury pathogenesis has still not been clearly defined. Most reports indicate a "bottom-up" progression of tissue damage [2]. Muscle is more sensitive to pressure damage than skin because it is the most metabolically active layer and is at the greatest risk for ischemic injury [8].

The capillary level is the end point of circulation. From the capillaries, oxygen and nutrients diffuse into the tissues, and carbon dioxide and waste products are removed. A collapsed capillary bed is nonfunctioning and useless to the tissues. The minimal amount of pressure required to collapse a capillary is referred to as the capillary closing pressure [1]. Studies have shown that an average of 32 mm Hg will collapse the arterial side of the capillary circulation, and 18 mm Hg of pressure will collapse the venous end. However, these values cannot be accepted as universal; capillary pressures vary among persons, sites, and times [2]. Furthermore, the studies that elicited these values were done on healthy adult males, not debilitated or elderly patients. Other studies have shown that the functional capillary pressure, the pressure needed to the keep the capillary bed open, is around 17 mm Hg. Extended pressure resulting in capillary collapse will cause tissue damage.

Shear is the result of gravity pushing down on the body and resistance (friction) between the patient and a surface, such as the bed or the chair, holding the skin in place [2]. For example, when the head of the bed is raised (e.g., high Fowler position), gravity facilitates forward slide, pulling the body down toward the foot of the bed. The skin on the patient's lower back and gluteal area resists the motion and is held in place by the bed's surface while the bones and tissues beneath the area begin to slide. This causes puckering of the skin, stretching and angulation of small vessels, impedance of blood flow, and traction on subcutaneous tissue and muscle. Left unchecked, the net effect may result in ischemic injury to tissues at the fascia layer. When the head of the bed is elevated more than 30 degrees, shear force occurs over the sacrum and coccyx. Shear injury is not usually visible at the skin level, but shear is responsible for much of the damage associated with initiation of pressure injuries [4]. The areas of the body most vulnerable to shearing forces are shoulder blades, elbows, sacrum, ischial tuberosities, and heels. Signs of shear injury include irregular deep lesions, undermining, and tunneling.

Prevention of Pressure and Shearing

There are several steps that may prevent the damage resulting from pressure and shear. If possible, limit the head of the bed elevation to 30 degrees or less. If the head must be elevated, the patient's knees may be bent ("gatched") with his or her feet flat on the bed. Using lift sheets to reposition patients is also recommended. Support surfaces are often utilized, and a low-resistance, breathable, and waterproof surface helps to eliminate friction. Foam surfaces lock the patient into place and reduce sliding. However, foam is not an appropriate surface to use if maceration (damage due to moisture trapped against the skin) is a problem [2].

When the patient is in a chair in sitting position, he or she should place feet flat on the floor and the back should be in alignment with the back of the chair. Consider using wheelchair or chair cushions that are higher in the front than the back for patients who tend to slide out of their chairs.

FRICTION

Friction occurs when one surface moves across another surface, such as when a patient's skin slides across a bed sheet. This can result in the "sanding away" of the epidermal layer and upper part of the dermis, resulting in abrasions [2; 8]. Friction injuries often present as erythema and tenderness followed by skin loss. Friction damage can be seen under restraints, braces, and on the elbows, or with repetitive rubbing or repetitive cleansing. Patients with uncontrollable movements or spasticity are also at high risk for friction injury, often referred to as "sheet burn." Friction injury occurs more frequently when the skin is fragile or macerated, and tissues subjected to friction are more susceptible to pressure injury damage, infection, and deeper ulceration [4; 8].

Prevention of Friction

As with pressure and shear, there are steps to minimize friction in at-risk patients. The most common involve measures to prevent the patient sliding down in bed (e.g., use of knee gatch on bed). All skin care measures should be gentle, no scrubbing or aggressive rubbing, and heel and elbow protectors should be utilized. Cornstarch may help to reduce the impact of friction.

MOISTURE

Moisture weakens the resilience of the epidermis to external forces. Maceration causes softening of the connective tissue, and a macerated epidermis erodes more easily. Overhydrated skin has decreased tensile strength. Skin can appear "waterlogged," with areas of denuded skin and fissure formation. Shear and friction are increased when there is a moderate amount of moisture present, but it has been reported that shear and friction decrease in the presence of high levels of moisture. The role moisture plays in pressure injury development is an area of on-going research [9; 10; 11; 12].

Major sources of moisture are incontinence, wound drainage, tube leakage, and sweating. Urinary and fecal incontinence expose the skin to excessive amounts of moisture and chemical irritation. There is a higher risk for skin breakdown with fecal incontinence than urinary incontinence because of the pathogens in stool.

Prevention of Excessive Moisture

Research has shown that when properly assessed and treated, urinary incontinence can be corrected in about 30% of nursing home residents [13]. Depending on the severity of the incontinence, the patient may be initiated in a toileting program. This consists of prompted voiding; specifically, the patient is taken to the bathroom at regular intervals and instructed to use the bathroom.

When this is not feasible (e.g., if a patient is unable to respond to instructions), the patient should be checked for incontinence every two to three hours and repositioned every two hours, with skin checks. Moisture barrier creams/lotions offer good protection for patients with incontinence. A folded, clean pillowcase between skin folds may also be used for moisture absorption.

For sweating, barriers are contraindicated, because they retain moisture against the skin. For patients for whom sweating is an issue, use non-caking powder or a non-occlusive moisture barrier [2].

Some patients will benefit from the use of absorptive products. All absorbent products are not equal, and their benefits must be evaluated according to the needs of the patient. Odor control, wicking properties, absorbency, comfort, and cost all must be considered.

The appropriate use of containment devices, such as condom catheters, should also be evaluated. Trauma related to incorrect application of condom catheters is common and correct sizing and application is important.

STAGES OF BREAKDOWN

When should a pressure injury be down staged?

Staging is an assessment system that classifies pressure injuries based on anatomic depth of tissue damage. As noted, in the 2016 revision to the NPIAP staging system, the term "pressure injury" replaced "pressure ulcer," to alleviate confusion between injury to intact skin (stages 1 and deep tissue injury) and open ulcers (stages 2–4 and unstageable pressure injury). At that time, NPIAP also updated the definitions of pressure injury stages (***Table 2***) and included the following changes [6]:

- Arabic numbers replaced Roman numerals in stages 1–4.
- The term "suspected" was removed from the deep tissue injury diagnostic label.
- Two additional pressure injury definitions (Medical Device-Related Pressure Injury and Mucosal Membrane Pressure Injury) were added.

Staging of a pressure injury can only occur after all necrotic tissue has been removed and it is possible to see the injury bed [1]. If this is not possible, the injury will be classified as unstageable. Pressure injury staging is not used to indicate pressure injury healing; a pressure injury should never be "down staged" or reverse staged (e.g., a pressure injury that is healing does not go from a stage 4 to a stage 3).

NPIAP PRESSURE INJURY STAGES	
Stage	**Definition**
Stage 1	Intact skin with non-blanchable redness of a localized area, usually over a bony prominence. Area may present with changes in sensation, temperature, or firmness, even before visual changes are noted. Darkly pigmented skin may not have visible blanching, but its color may differ from the surrounding areas.
Stage 2	Partial thickness loss of dermis presenting as a shallow open injury with a red/pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled blister.
Stage 3	Full thickness tissue loss. Subcutaneous fat may be visible, but bone, tendon, or muscle is not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunneling.
Stage 4	Full thickness tissue loss with exposed bone, tendon, or muscle. Slough or eschar may be present on some parts of the wound bed. Often include undermining and tunneling.
Unstageable pressure injury	Full thickness tissue loss in which the base of the injury is covered by slough (yellow, tan, gray, green, or brown) and/or eschar (tan, brown, or black) in the wound bed.
Deep tissue pressure injury	Persistent non-blanchable, deep red, purple, or maroon area of discolored, intact or non-intact skin or blood-filled blister. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer, or cooler as compared to adjacent tissue.
Medical device-related pressure injury	Describes the cause of a pressure injury resulting from and taking shape of a medical device. Use staging system to classify.
Mucosal membrane pressure injury	Injury found on mucous membranes in a location in which a medical device was used. Cannot be staged.

Source: [6] *Table 2*

In pressure injury healing there is no regrowth of lost muscle, subcutaneous fat, or dermis; instead, the wound is filled in with scar tissue. Therefore, reverse staging does not accurately reflect the physiologic changes occurring in the pressure injury. When a stage 4 injury has healed, it should be classified as a healed stage 4 pressure injury [4].

Stage 2 pressure injuries have a healing time that ranges from 8.7 to 38 days. Stage 3 and stage 4 pressure injuries can take up to 69 days to heal. Healing rates are lower for stage 3 and stage 4 injuries than for stage 2 injuries in all healthcare settings [6]. Irreversible tissue damage can happen in as little as two hours in a patient with low tolerance; however, the injury may not become apparent for two to five days.

Stage 1

Stage 1 pressure injury presents as persistent redness in intact skin. If the area is pressed, it will not lighten in color (non-blanchable) [14]. It usually occurs in a localized area over a bony prominence, and this area can be painful, firm, soft, and warmer or cooler than the surrounding tissue [6]. This area of redness has a clear but possibly irregular boundary [14]. In darker skin tones, blanching may not be visible and the color may differ from the surrounding area [6]. In these instances, it is important to look for the other signs of pressure injury, such as pain, change in temperature, and changes in skin texture.

Stage 2

Stage 2 pressure injury presents as shallow, open wounds with partial loss of the dermis. The wound bed is pink/red and without slough. A stage 2 pressure injury may also present as a serous fluid-filled blister [6]. Fat and deeper tissues are not visible, and slough and eschar are not present. These injuries are most commonly seen on the sacrum due to moisture and shear, and on the heel due to shear [6]. Skin tears, tape burns, incontinence-associated dermatitis, maceration, or excoriation of the skin should not be classified as stage 2 pressure injuries [4].

Stage 3

Stage 3 is full thickness tissue loss. Subcutaneous fat may be visible and rolled wound edges are often present, but bone, tendon, and muscle are not exposed. There may be slough in the wound, but it does not obscure observation of the wound bed; if slough or eschar obscures the observation, this is an unstageable pressure injury. Tunneling and undermining may be present [6]. It is important to remember that the depth of stage 3 pressure injuries will differ from one location to another. For example, the bridge of the nose, ear, occiput, and malleolus do not have a subcutaneous layer, and in these areas a stage 3 pressure injury can be shallow [6].

Stage 4

Stage 4 injuries are characterized by full thickness tissue loss with exposed bone, tendon, or muscle. These injuries often include undermining and tunneling, and rolled wound edges are often seen [6]. Slough and eschar may be present in part of the wound bed; however, if slough or eschar obscures the observation, this is an unstageable pressure injury [14]. In some cases, stage 4 pressure injuries can affect supporting structures and may lead to osteomyelitis. As with stage 3 injuries, the depth of the injury will vary by anatomical location.

Unstageable Pressure Injury

A wound that is unstageable is defined as having full thickness tissue loss in which the base of the injury is covered by slough (yellow, tan, gray, green, or brown) and/or eschar (tan, brown, or black) [6]. Until the base of the wound can be visualized, the wound will remain unstageable. A necrotic wound cannot be staged until the necrotic tissue has been debrided, and it is then that a stage 3 or stage 4 injury will be revealed [6]. It is also important to remember that it is clinically inaccurate to stage a granulating wound if it is the first assessment, as visualizing the depth of the actual pressure sore is not possible [4]. In addition, if stable eschar on an ischemic limb or the heel(s) is present, it should not be removed [6].

Deep Tissue Pressure Injury

Deep tissue pressure injury, previously suspected deep tissue injury, is a pressure-related injury, much like a bruise, that is characterized by persistent non-blanchable, deep red, maroon, purple discoloration or epidermal separation revealing a dark wound bed or blood-filled blister. Deep tissue pressure injuries can present on either intact or non-intact skin. This type of injury is caused by intense and/or prolonged pressure and/or shear. Deep tissue pressure injury may resolve without tissue loss or may rapidly change to reveal the extent of the tissue injury. If necrotic tissue, subcutaneous tissue, granulation tissue, fascia, muscle, or other underlying structures are visible, this indicates a full thickness pressure injury (Unstageable, stage 3, or stage 4). The NPIAP does not recommend using deep pressure tissue injury to describe vascular, traumatic, neuropathic, or dermatologic conditions [6].

Color is the key to differentiating between deep tissue injury and a stage 1 pressure injury. Purple or maroon areas indicate deep tissue injury; non-blanchable redness is characteristic of stage 1 injuries. Deep tissue injury can become a stage 3 or a stage 4 pressure injury even with optimal care [6]. In general, the most common areas of involvement are the heels and sacrum. In some patients, particularly those who are debilitated, deep tissue injury can develop rapidly [14].

Medical Device-Related Pressure Injury

Medical device-related pressure injuries describe injuries or ulcers that result from the use of devices designed and applied for diagnostic or therapeutic purposes. The injury is generally in the shape or pattern of the device and should be staged using the staging system [6].

Mucosal Membrane Pressure Injury

Mucosal membrane pressure injury is found on the mucous membranes. This type of injury is typically attributed to use of a medical device on a mucous membrane, and due to the nature of this type of tissue, these injuries cannot be staged.

PRESSURE INJURY RISK ASSESSMENT

Identifying patients at risk for pressure injuries is vitally important as it allows for preventative measures to be initiated. Elements of prevention include identifying individuals at risk for developing pressure injuries, maintaining skin integrity, treating the underlying causes of the injury, relieving pressure, assessing the total state of the patient to correct any deficiencies, and patient/family education.

MAJOR RISK FACTORS IN PRESSURE INJURY DEVELOPMENT

Decreased Mobility

Immobility is possibly the greatest risk factor for pressure injury development [4]. According to the United Spinal Association, up to 80% of patients with spinal-cord injuries will develop pressure injuries during their lifetime and 30% will have more than one pressure injury [15]. Patients who have lost the ability to ambulate, either for physical or cognitive reasons, will commonly develop pressure injuries while chair- or bedridden. The prevention of injuries in these patients is a vital aspect of ensuring an optimal quality of life.

Contractures

Untreated contractures often lead to pressure injury development. Contracted limbs, usually caused by continued hypertonic muscle or tendon stress, can exert pressure on surrounding tissues and adjacent areas. Contracture of a leg or foot can result in pressure injury development in that extremity, because it exerts more pressure on the support surface than a normal extremity.

Decreased Sensation

The sensory receptors, cortex, and motor neurons/muscles act as a sort of "pressure injury prevention system." These sensations induce individuals to move or shift position when an uncomfortable sensation is experienced. Injury or disease to any component of this system results in a loss of these protective reflexes. Therefore, patients who cannot feel discomfort or cannot sense ischemia are at high risk for pressure injury development.

Perfusion Status

Adequate circulation is needed to maintain tissue health by delivering oxygen and nutrients to the cells and removing waste products. Edema reduces tissue perfusion by increasing the distance between the cells and the capillary network. Normal, healthy tissue (in a person with normal sensation and movement) can tolerate short periods of ischemia because tissues require intermittent rather than continuous blood flow [2]. However, extended periods of ischemia can result in tissue damage and, with regard to skin, can lead to pressure injuries.

Hypotension

Low arterial blood pressure (hypotension), defined as systolic blood pressures less than 100 mm Hg and diastolic pressures less than 60 mm Hg, has been linked to increased risk for pressure injury development. In response to hypotension, the body redirects blood flow to the vital internal organs at the expense of the peripheral vascular system, which serves the skin. As the perfusion level drops so does the skin's ability to tolerate external pressure. Capillaries subsequently close at lower levels of interface pressure, and there is an increased risk of damage due to ischemia [1].

Hydration

Normal skin hydration is provided by an intact stratum corneum and sebum secretion. Factors that can decrease skin hydration are overly vigorous or frequent washing, low environmental humidity, and aging. The removal of sebum by frequent cleansing or bathing can cause dehydration. It is important to use moisturizing lotion, particularly immediately after bathing to moisten skin.

Cognition

Loss of cognition is also associated with increased risk for pressure injuries. Impaired mental status leads to a lack of awareness of discomfort or pressure and may be associated with incontinence. The ability to respond appropriately or to inform others of the need for assistance is often lost completely.

Stress

Stress is a primitive response to injury or anticipated injury. Research has shown that during periods of stress, blood vessels in the peripheral tissues constrict. In a study designed to mimic the body's response to stress, healthy subjects were given an infusion of exogenous epinephrine [1]. The increased levels of epinephrine decreased the levels of subcutaneous tissue oxygen by 45%. Other studies have shown that psychologic stress has a negative impact on healing [1].

Depression

The National Institute of Mental Health estimates that 8.4% of adults in the United States are suffering from depression, and major depression is the leading cause of disability worldwide [16]. Depression is particularly under-recognized in the elderly. Depressed patients have little interest in self-care and nutrition, both of which may predispose an individual to pressure injuries [4].

Age

Patients older than 65 years of age experience pressure injuries most frequently [1]. With aging, the skin becomes more fragile. The skin layers adhere less securely to each other and often appear paper thin and almost transparent. There is also evidence of increased dryness, decreased vascularization, and increased vascular fragility.

In elderly individuals, there is a decrease in surface barrier function. The ability of the soft tissue to evenly distribute the mechanical load without compromising blood flow is impaired. There is less subcutaneous tissue to cushion boney prominences. This, in addition to decreased sensory perception, makes elderly skin more vulnerable to pressure, shear, and friction [2]. Research has shown that, in the geriatric population, blood flow in the area of the ischial tuberosity while sitting on an unpadded surface is lower than in younger adults [4].

Although much less common, children can also develop pressure injuries. Most commonly, these injuries develop in the occipital region in infants and toddlers and on the sacrum in young children [1].

Obesity

What type of "unusual" pressure injuries occur more often in obese patients?

In the United States, an estimated 42.5% of adults 20 years of age and older are obese and 9.0% are morbidly obese [17]. Obesity is defined as a body mass index (BMI) of 30 or greater; severe or morbid obesity is defined as a BMI greater than 40 [17].

Factors that contribute to pressure injury development in obese individuals include decreased blood supply in adipose tissue, difficulty in turning and repositioning, moisture within skin folds, incontinence, skin-to-skin friction, immobility, and poor nutrition. Obese patients are particularly at risk for "unusual" pressure injuries resulting from pressure within skin folds. Obese patients may have large panniculi ("aprons"), weighing up to 50 pounds. The abdominal panniculus must be regularly repositioned in order to prevent pressure injury. This may be accomplished by placing the patient in the side-lying position and lifting the panniculus away from the underlying skin surface, which allows air to the area and simultaneously relieves pressure.

Tubes or catheters can also cause pressure by burrowing into skin folds. Poorly fitting beds, chairs, or wheelchairs may also be a source of pressure [18].

Nutrition

Low body weight and impaired nutrition are also concerns. Weight less than 119 pounds or a BMI less than 20 are indicators of increased risk for pressure injury development [19].

Recent weight loss, decreased nutritional intake, inadequate dietary protein, and impaired ability to feed oneself have been identified as risk factors for pressure injury development. An estimated 50% of elderly patients admitted to the hospital have suboptimal protein nutrition [19]. When there is a sustained deficit of protein as an energy source, skin and soft tissues become more vulnerable to injury. Low protein levels also result in decreased resistance to infection. Older adults also have increased incidence of low calorie intake and low levels of zinc and vitamin B12.

Vitamin A, C, and E deficiencies have been associated with pressure injury formation. Vitamin A works in the body to maintain epithelial integrity and is involved in collagen synthesis. It also plays a role in protection against infection. A deficiency of vitamin A can inhibit collagen synthesis, delay re-epithelialization, and decrease cellular cohesion. Vitamin C is also involved in collagen synthesis, immune function, and wound repair. A deficiency of vitamin C can result in capillary fragility. Vitamin E deficiency often decreases the immune function of the skin.

Diabetes

It is estimated that 11.3% of the U.S. population has diabetes [20]. Alone, diabetes increases the risk for pressure injury development by 56% [19]. However, approximately 27% of diabetics in the United States are 65 years of age or older, which compounds the risks [21].

Elevated blood sugar levels characteristic of diabetes result in decreased phagocytic ability of neutrophils and diminished wound strength. Patients with diabetes are more prone to infection, and wound healing is slower in this population than in patients without diabetes. Hyperglycemia can also result in protein-energy malnutrition, dehydration, and alteration in microcirculation [1]. Peripheral neuropathy, a common complication associated with diabetes, results in decreased sensation, an established risk factor for pressure injuries.

Smoking

Nicotine impedes blood flow to the tissues in two ways: it is a potent vasoconstrictor, and it increases the adhesiveness of platelets, resulting in clot formation. Carbon monoxide contained in cigarette smoke prevents oxygen from attaching to the hemoglobin molecule. This significantly reduces the amount of oxygen circulating in the blood stream. The same reaction occurs to some extent in people exposed to secondhand smoke. Studies have shown that cigarette smoking is associated with a higher incidence of pressure injury development in spinal cord-injury patients [22]. Patients who smoke also have a higher rate of recurrence of pressure injuries [4].

Medications

Several medications can affect skin integrity. Normal skin flora can be altered by antibacterials, oral steroids, and hormones. Additionally, analgesics, antihistamines, nonsteroidal anti-inflammatory medications, and chemotherapy can alter inflammatory reactions. Of these, corticosteroids have been studied the most extensively. Corticosteroids interfere with collagen synthesis and epidermal regeneration at a dose of 40 – 60 mg per day [2].

Other Risk Factors

Areas of advanced pressure injuries that have healed are more likely to have recurrent breakdown. Therefore, documentation of history of a healed injury and its stage, if known, is important. Several other conditions can interfere with systemic and peripheral oxygenations and nutrition, resulting in pressure injuries. These conditions include:

- Respiratory problems
- Atherosclerosis
- Coronary artery disease
- Peripheral vascular disease
- Congestive heart failure
- Malignancies
- Human immunodeficiency virus/ acquired immune deficiency syndrome
- Anemia
- End-stage renal disease
- Thyroid disease
- Terminal illness
- Patient refusal of some aspects of care and treatment

RISK ASSESSMENT

What is the most reliable tool for identifying patients at risk for pressure injury breakdown?

No step is more important in preventing pressure injuries than understanding a patient's risk. Risk assessment is used to identify:

- Populations at risk
- Level of risk
- Type of risk

THE NORTON SCALE FOR PREDICTING PRESSURE INJURY RISK					
Score	**Physical Condition**	**Mental Condition**	**Activity**	**Mobility**	**Incontinent**
4	Good	Alert	Ambulant	Full	Not
3	Fair	Apathetic	Walk-help	Slightly limited	Occasional
2	Poor	Confused	Chair-bound	Very limited	Usually-urine
1	Very bad	Stupor	Stupor	Immobile	Doubly

Source: [24] *Table 3*

A risk assessment is a way of attaching numbers and specifics to identified risk factors. An informal risk assessment cannot take the place of a formal risk assessment, such as the one conducted using the Braden Scale. Research shows that without formal risk assessment, clinicians tend to intervene consistently only at the highest levels of risk [23]. In some studies, repositioning or turning, an important part of pressure injury prevention, was prescribed for fewer than 50% of the patients at mild-to-moderate risk for pressure injury development [4].

EVIDENCE-BASED PRACTICE RECOMMENDATION

When conducting a pressure injury risk assessment, the National Pressure Ulcer Advisory Panel, the European Pressure Ulcer Advisory Panel, and the Pan Pacific Pressure Injury Alliance recommend using a structured approach, including a comprehensive skin assessment, supplementing use of a risk assessment tool with assessment of additional risk factors, and interpreting the assessment outcomes using clinical judgment.

(https://www.internationalguideline.com/static/pdfs/Quick_Reference_Guide-10Mar2019.pdf. Last accessed May 9, 2022.)

Level of Evidence: Good Practice Statement (The recommendation is not supported by a body of evidence but considered to be significant for clinical practice.)

The Braden Scale

The Braden Scale was developed in 1987 by Barbara Braden and Nancy Bergstrom [23]. Since then, it has undergone testing in several clinical settings, and its validity has been established by expert opinion. It is considered one of the most reliable tools for identifying patients at risk for pressure injury development, and it is the most widely used. The Braden Scale scores factors that contribute to prolonged pressure and factors that result in diminished tissue tolerance for pressure [23]. There are six items scored in the assessment [23]:

- Sensory perception
- Moisture
- Activity
- Mobility
- Nutrition
- Friction and shear

Each item is scored on a scale between 1 and 4 with the exception of friction and shear, which is scored between 1 and 3. The lower the score, the more severe the impairment or problem in that area. Therefore, the lower the score, the higher the patient's risk for pressure injury development. Various studies have shown cut-off scores from 16 to 18 as being at risk [2]. Although cut-off scores vary, usually a score of 13–14 is considered moderate risk, 10–12 indicates high risk, and 9 or less is very high risk.

The Braden Scale should be used for assessment on admission to a care facility or after return from a hospital. Research shows that a repeat assessment done 48 hours to 72 hours after admission further defines pressure injury risk. In nursing home populations, the majority of pressure injuries develop during the first two weeks following admission [1]. In addition, most facilities set their own policies regarding reassessment frequency (e.g., quarterly). However, it is important to note that any change in a patient's condition warrants reassessment.

Braden Scale assessment is completed by licensed personnel familiar with the patient and is shared with all staff caring for the patient; good communication is essential to ensure a meaningful assessment [4]. Licensed and unlicensed staff must have a basic knowledge of Braden scores and how it directs patient care. Accuracy of scoring is very important to determining the appropriate intervention.

The Norton Scale

The Norton Scale was developed in the 1960s and is used to assess the risk for pressure injury in adults (***Table 3***). The five items in the assessment are scored from 1 to 4, with 1 indicating a low level of functioning and 4 indicating the highest level of functioning. A score of 14 or less generally indicates the patient is at risk [24].

The Norton Scale should be used in conjunction with the clinical assessment [24].

SKIN AND PAIN ASSESSMENTS

Admission assessment is the foundation for effective prevention and initiation of a management program. All special garments, including shoes, heel and elbow protectors, orthotic devices, restraints, and protective wear, should be removed during a skin inspection. If immobilizers or splints are being used, the physician should be consulted to ensure that they may be safely removed. If they cannot be removed, this should be documented in the patient's record.

It is also important to incorporate a holistic assessment, evaluating the meaning and significance of skin breakdown and wound development to the patient and his or her caregiver. Does the patient view the injury as a sign of vulnerability, a loss of independence, or an unavoidable consequence of aging?

There are several goals of completing a skin assessment. Foremost, it is imperative to identify and assess areas of impending or actual skin breakdown and patients at risk for future skin injuries and immediately begin appropriate management interventions. For patients at high risk for pressure injury development, a systemic skin assessment should be conducted at least daily and findings should be documented.

ELEMENTS OF A BASIC SKIN ASSESSMENT

A basic skin assessment includes evaluation of the temperature, color, moisture, turgor, and integrity of the skin. The skin's response to pressure indicates its condition. Pressure to soft tissue interrupts the blood flow to that area and results in pallor to the overlying skin. This pallor indicates tissue ischemia. When the pressure stops, the skin should quickly return to its normal color as blood flow returns [25]. In general, when pressure is relieved from an area, redness will resolve within 30 minutes if there is no tissue damage. Therefore, it is important to recheck areas of redness 30 minutes after pressure is relieved and to document findings.

All aspects of the assessment should be explained to the patient. Many people are shy about exposing their body to strangers, even to clinicians. Conduct the exam in a warm and private room with good lighting. It is vital not to rush or overlook part of the assessment, even if the patient is restless.

Although a head-to-toe assessment is often used, a toe-to-head assessment may result in less likelihood of missing areas of potential or actual breakdown, considering that a thorough inspection of the feet and heels is often overlooked. When completing a toe-to-head skin assessment, start with the tips of the toes, between the toes, soles of the feet, back and sides of the heels, and inner and outer areas of both ankles. Continue up the following assessment sites:

- Right and left lower legs
- Right and left knees' inner and outer surfaces
- Right and left thighs
- Right and left ischial tuberosity
- Right and left hip
- Right and left iliac crest
- Sacrum
- Coccyx
- Lower, mid, and upper back
- Right and left shoulders
- Right and left ears (particularly redness under oxygen tubing)
- Back of the head

ASSESSING AND DOCUMENTING A PRESSURE INJURY

What should be included in the assessment of a pressure injury?

Documentation of a pressure injury should include location, stage (per NPIAP definitions), wound description (e.g., size, color, drainage), and pain level. Wound size should always be recorded in centimeters. The length is the longest head-to-toe measurement, while the width is the longest hip-to-hip measurement. The best practice recommendation is to measure the wound at the point of greatest length and the point of greatest width. Wound depth is measured by gently inserting a pre-moistened, sterile cotton swab into the deepest part of the wound. The measurement from the tip of the applicator to the level of the skin surface is recorded as the depth [4].

Undermining and/or tunneling should also be recorded in centimeters. Undermining is defined as tissue destruction underlying the intact skin along the wound margins, meaning the wound margins have separated from the wound. Using the face of the clock as a reference for location, with the patient's head representing 12 o'clock, measure the extent of the undermining clockwise. For example, undermining along the right and bottom borders may be recorded as extending 1.5 cm from 2 o'clock to 7 o'clock [26].

Tunneling refers to channeling that extends from any part of the wound and may pass through subcutaneous tissue and muscle. It may result in dead space and abscess formation. The depth of the tunnel should be measured with a sterile cotton swab and recorded. The direction of the tunnel should be documented using the clock method (e.g., 4 cm at 5 o'clock). If there is more than one sinus tract/tunnel, number each one clockwise [4].

It is also vital to assess and document the appearance of the wound bed. If the wound bed has a mixture of tissue in it, this should be documented by an approximate percentage (e.g., the wound base is 75% granulation tissue and 25% slough). Granulation results in "beefy" red tissue with a shiny, moist granular appearance, while necrotic tissue is gray, brown, black, and moist. Eschars are typically gray to black and dry or leathery in appearance [26]. Slough tissue is yellow/white to gray in color. It may be stringy or thick and appear as a layer over the wound bed [26]. Epithelial tissue will often begin to grow in from the edges over the wound surface. This tissue is generally pink and shiny. As a quick reference color guide, red is associated with normal healing, yellow indicates slough or dead tissue, and black is necrosis [4].

Wound drainage is another important aspect of pressure injury assessment. The amount should be noted (scant, moderate, or copious). The color and consistency of the drainage may be serous (clear or light yellow in color, thin, watery), sanguineous (red, thin), serosanguineous (pink to light red, thin, watery), or purulent (creamy yellow, green, white, or tan, thick, opaque). The presence of any associated odor should also be documented. A non-infected wound produces little or no odor. The impact of wound odor can be quite devastating to the patient and his or her family.

The area up to 4 cm from the edge of the wound circumferentially should be assessed. Describe its characteristics, particularly color and integrity. Circumferential redness up to 2 cm is indicative of cellulitis [1]. The skin around the pressure injury should be palpated to determine if it is soft or indurated. Indurated (hard) tissue, even in the absence of redness, is an indication of infection.

ASSESSING PAIN

Pressure injuries can cause considerable pain and suffering. Pressure injury pain has been described as ranging from sore to excruciating. In one study of patients with stage 2–4 pressure injuries, 74% of patients rated their pain as mild, discomforting, or distressing; 19% rated their pain as horrible or excruciating [27]. Pain and odor control are a major concern for patients, and studies have shown that patients rank pain control as more important than healing [4]. The level of pressure injury pain depends both on the stage of the injury and on manipulation of the area (e.g., if a dressing change is done at the time of assessment). The majority of patients report pressure injury pain at rest as well as with dressing changes. Pressure injury pain may be due to tissue trauma from sustained loads, inflammation, damaged nerve endings, infection, procedures such as debridement, and dressing changes [27].

The gold criterion for assessing pain intensity is self-reporting and the utilization of standard pain intensity instruments. Two of the most widely used pain assessment scales are the numeric pain intensity scale and the Wong-Baker Faces Pain Rating Scale [28]. The numeric pain intensity scale consists of ratings from 0 (no pain) to 10 (worst possible pain). This scale can be used for pain assessment with adults and children older than 7 years of age [29]. Visual presentation of the numeric pain intensity scale is helpful with hearing impaired patients, and the scale has been translated into many languages.

The Wong-Baker Faces Pain Rating Scale consists of six faces ranging from a happy smiling face (no pain), to a crying, frowning face (worst pain). The patient is asked to choose the face that best reflects his or her pain. The Faces Pain Rating Scale is the preferred scale for use with children and may also be used with the geriatric population. It can also be used with cognitively impaired patients and those for whom English is a second language.

After the initial pain assessment has been completed, reassessment should be done at regular intervals. Pain intensity should be rated by the patient, not a healthcare professional. The following questions may be used to help determine patients' pain levels:

- What kind of pain are you experiencing?
- What word(s) would you use to best describe it (e.g., burning, aching, shooting)?
- What makes the pain better?
- What makes it worse?
- Where is the pain located?
- Does the pain radiate?
- Would you describe your pain as none, mild, moderate, severe, or excruciating?
- How would you rate your pain on a scale of 0 to 10, with 0 representing no pain and 10 being the worst imaginable pain?
- What is the pain intensity at its worst, best, and now?
- Is the pain better or worse at any particular time of the day or night?
- When does it start and when does it stop?
- Pain Management

The goal of pain management in the patient with pressure injury is to eliminate the cause of pain and to provide analgesia. There are several interventions and practice modifications that can prevent or manage pressure injury-associated pain.

Skin care and assessments should be performed at a time of day when the patient is less fatigued [14]. All procedures should be thoroughly explained before they are performed. If a patient has questions, this should be addressed, and healthcare professionals should be encouraging and provide positive reinforcement. It is important to avoid trauma (shearing and tear injuries) to fragile skin during transferring, positioning, or holding a patient. If necessary, adjunctive medications may be administered to improve sleep and reduce anxiety, which can contribute to experiences of pain.

Dressing changes are often very painful. An analgesic may be administered 30 minutes before dressing changes, and if possible, the number of daily dressing changes should be kept to a minimum. Tape should always be avoided on fragile skin. If patients are able, they should be allowed to remove their own dressings or set the pace of dressing changes. All patients should be assessed for pain before, during, and after dressing changes, and these findings must be documented [4].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Pressure Ulcer Advisory Panel, the European Pressure Ulcer Advisory Panel, and the Pan Pacific Pressure Injury Alliance recommend clinicians consider applying a topical opioid to manage acute pressure injury pain, if required and when there are no contraindications.

(https://www.internationalguideline.com/static/pdfs/Quick_Reference_Guide-10Mar2019.pdf. Last accessed May 9, 2022.)

Level of Evidence: B1 (The recommendation is supported by level 1 studies of moderate or low quality providing direct evidence or level 2 studies of high or moderate quality providing direct evidence)

Physical therapy and occupational therapy may be helpful to decrease contractures and muscle spasm. Of course, ensuring proper seating and positioning can improve pain scores as well as decreasing the risk for further pressure injuries.

INDIVIDUALIZED PROGRAM OF SKIN CARE

One of the most important steps to prevent pressure injuries is physically repositioning the patient frequently. Repositioning should be done every one to two hours, depending on the patient's condition [2].

POSITIONING IN BED

Every time the patient is repositioned, look for areas of redness and make sure that the new position does not put weight on these areas. Avoid massaging reddened areas over bony prominences [14]. Donut-shaped supports or ring cushions that encircle the ischemic areas should not be used as they can reduce blood flow to an even wider area of tissue. To the degree that the patient is able, encourage activity. Even a few steps done frequently will help. It is important to maintain current activity level, mobility, and range of motion. When repositioning the patient in bed, it is essential to avoid the 90-degree side-lying position. This position puts intense pressure directly over the trochanter. Instead, use the 30-degree lateral position, utilizing a pillow or foam wedge to maintain the position [14]. Keeping the head of the bed at 30-degrees or less (if medically feasible) will help prevent shear. Place a pillow between the patient's knees or ankles to minimize pressure where one limb lies on top of the other. Lifting devices, such as an overhead trapeze or bed linen, are helpful when moving patients. It is important to minimize dragging during transfers and position changes. Minimize environmental factors leading to skin drying, such as low humidity (less than 40%) and exposure to cold [4]. Posting an individualized turning schedule in patient rooms can be helpful to healthcare professionals and patients.

Heel injuries are especially painful and are among the most difficult to heal. Heel pressure injuries can develop infection and, in extreme cases, may lead to amputation of the foot. To prevent the development of pressure injuries on the heels, place a pillow under the calf to float the heels off the bed. There are also devices available that eliminate pressure on heels and prevent foot drop (e.g., suspension boots). Current guidelines state that heels are to be kept off the bed [2; 30].

POSITIONING WHILE IN CHAIR

Pressure injuries are a particular concern for patients who spend a significant amount of time in chairs. A patient is more likely to develop pressure injuries from sitting than from reclining, as sitting puts the patient's weight on the relatively small surface areas of the buttocks, thighs, and soles of the feet. Much of this weight is focused over the small area of tissue covering the ischial tuberosities. It is important for patients who sit in a chair to regularly change position. A dependent patient must have his/her position changed in a chair at least every hour. Patients who are able to move themselves should shift their weight (even slightly) every 15 minutes.

A patient should be properly positioned in a chair for postural alignment, distribution of weight, balance, and stability. Patients should sit with their back erect and against the back of the chair, thighs parallel to the floor, knees comfortably parted, and arms horizontal and supported by the arms of the chair. This position distributes weight evenly over the available body surface area. Slouching can cause shearing and friction and places undue pressure on the sacrum and coccyx. Feet should be kept flat on the floor to protect the heels from pressure and distribute the weight of the legs over the largest available surface area. The thighs and arms should remain parallel to ensure that weight is evenly distributed instead of being focused on the ischial tuberosities and elbows. Parting the knees will prevent the knees and ankles from rubbing together. If a patient uses a footstool, it is vital that his or her knees are not above hip level, because this shifts the weight from the back of the thighs to the ischial tuberosities. This same problem can occur if the chair is too short for the patient.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Pressure Ulcer Advisory Panel, the European Pressure Ulcer Advisory Panel, and the Pan Pacific Pressure Injury Alliance recommend using a pressure redistribution cushion for preventing pressure injuries in people at high risk who are seated in a chair/wheelchair for prolonged periods, particularly if the individual is unable to perform pressure-relieving maneuvers.

(https://www.internationalguideline.com/static/pdfs/Quick_Reference_Guide-10Mar2019.pdf. Last accessed May 9, 2022.)

Level of Evidence: B1 (The recommendation is supported by level 1 studies of moderate or low quality providing direct evidence or level 2 studies of high or moderate quality providing direct evidence)

CLEANSING AND BATHING

What are the properties of appropriate skin cleansing agents?

Maintaining skin cleanliness and moisturizing frequently can protect skin integrity. The skin should be cleaned with water and a gentle soap, preferably a pH-balanced cleanser. Alkaline products remove skin lipids, which increases water loss and weakens the barrier function of the skin [14]. Avoid hot water for bathing and scrubbing or using harsh cleaning agents. A soft cloth should be used to pat rather than rub the skin dry. Thromboembolic deterrent (TED) stockings should be removed when bathing, and the nurse or physician should be notified of any redness, discoloration, or skin breakdown.

It is important to individualize the frequency of skin cleansing based on the patient's age, skin texture, and dryness or excessive oiliness of the skin. A daily bath may not be needed for all patients.

MOISTURIZING THE SKIN

The epidermis is about 30% water, but through a process called trans-epidermal water loss, skin can lose its natural moisture. Without sufficient moisture, skin can become dry, brittle, and vulnerable to breakdown [2]. Therefore, products should be used to keep the skin supple.

Emollients, such as mineral oil, petrolatum, and lanolin, penetrate into the stratum corneum to increase the lipid component and add softness to the skin. In addition, the oil film on the skin surface prevents water loss and helps to rehydrate the stratum corneum [14].

Moisture barriers such as dimethicone also help to prevent water loss and to retain lipids and water within the skin cells. These products maintain the "brick and mortar" configuration of the skin by replacing lost "mortar" [2].

Humectants, such as glycerin, urea, and Lac-Hydrin, increase the water content of the stratum corneum by pulling water from the environment. Normal hydration of the skin cells maintains normal cell shape and cell function. All moisturizers should be applied to clean, slightly moist skin. Special attention should be paid to bony prominences, heels, ears, and the back of the head.

BOWEL AND BLADDER MANAGEMENT

Urinary and Fecal Incontinence

According to the National Association for Continence, approximately 25 million Americans have transient or chronic incontinence. It is estimated that more than 90% of patients with urinary incontinence fail to seek medical intervention or treatment [31].

At least half of all nursing home residents experience urinary incontinence [31]. For patients who are cooperative and aware of bladder filling, a toilet program should be instituted, including planned voiding every two hours. For patients who are uncooperative or unaware of bladder filling, consider the use of absorptive products or condom catheters for men. It is important to use diapers and underpads that wick moisture away from patients' skin. These patients should be checked for incontinence every two hours. Incontinent patients should be cleaned as soon as possible after soiling using specialized incontinence skin cleansers or soaps.

For patients with fecal incontinence and severe diarrhea, all potential causative factors should be explored and addressed. A rectal pouch may be useful for these patients. In cases of chronic incontinence, an every-other-day suppository or enema may be considered. In addition, barrier ointments help protect the skin from incontinent episodes. If used, apply a thick coat of ointment, wipe off the soiled top layer, and apply another layer. Do not clean off the paste to skin level when bathing or cleaning.

SUPPORT SURFACES

There is a vast array of support surfaces and seating options available, but as helpful as these devices may be, they are no substitute for attentive care. Patients still require individualized turning schedules regardless of the equipment used.

Most support surfaces reduce pressure by conforming to the contours of the body so pressure is redistributed over a larger area rather than concentrated in one location [2]. There are many support options, including mattresses, overlays, and cushions.

Mattresses and Overlays

Most pressure relief mattresses use some form of foam, gel, or water to cushion the patient. Water mattresses and some air mattresses evenly distribute pressure under the patient. Low-air-loss and high-air-loss mattresses are specialized support devices that pass air over the patient's skin and promote evaporation [2].

The most common mattress overlays are foam, air, and gel. Foam overlays should be at least 3 inches thick for the average patient; even thicker is better. Two-inch foam overlays may add comfort, but they are not suitable for patients at risk for pressure injuries. Standard egg-crate mattresses are used for comfort only [2]. All support surfaces, regardless of the medium, function best with less linen between the patient and the surface. If a patient's weight completely compresses a mattress overlay, it is not effective. To make sure that a mattress is not "bottoming out," slide one hand between the mattress overlay and the mattress. If the patient's body can be felt through the overlay, it should be replaced [9]. The weight limit for most support surfaces is about 350 lbs. Special low-air-loss mattresses are available for patients who weigh more than 350 lbs.

An important factor in air-filled overlays is inflation; they may not be effective in preventing pressure injuries if they are over-inflated, under-inflated, or punctured. Therefore, inflation must be checked daily.

Patients must be comfortable and able to sleep on the support surface. Some surfaces produce noise that may not be tolerable for some patients.

Cushions

Products designed to help prevent pressure injuries while sitting fall into two broad categories: those that relieve pressure and those that make repositioning easier.

Seat cushions may be used to distribute weight over the largest possible surface area. These are generally made of foam, gel, air, or a combination [2]. Wheelchair cushions for short-term use are foam, air, water, or gel. The goal of these products is to improve weight distribution cost effectively. Gel and air cushions have been shown to be the most effective [14]. Wheelchair-bound patients who require long-term solutions need cushions that fit the wheelchair, support seating stability, provide high-level pressure reduction, and reduce shear. All cushions should be checked and repaired or replaced on a regular basis.

PATIENT/FAMILY EDUCATION

A vital component of a pressure injury prevention program is education. If possible, pressure injury prevention should not be a passive process for the patient and his/her family members. Rather, it should be a dialogue in which the patient or family feels comfortable asking questions and discussing problems. Patients should have as much control as possible in the plan of care. Empowerment is very important in maintaining the patient's physical and emotional well-being. The plan of care should be explained thoroughly to cognitively aware patients and their family.

At the same time, it is vital to evaluate the patient's/family's existing knowledge regarding pressure and pressure injuries. Healthcare professionals should show patients what they can do to facilitate pressure relief (e.g., how to make small position changes while in the chair). If possible, it is often beneficial to teach patients how to do simple range-of-motion exercises. Take time to train the patient as often as is appropriate; not everyone will absorb the information the first time it is heard [4]. It is important not to let noncompliance or a bad attitude from the patient or family discourage the teaching process. The subject should be approached as often as is reasonable. Include the family members and caregivers in the instructions. As well as assisting with care, they can encourage compliance. All efforts at patient and family/caregiver education should be documented, along with the patient's response (both verbal and behavioral).

STAFF EDUCATION

Education of caregivers is also a key factor in the prevention of pressure injuries and in the successful management of existing pressure injuries. All healthcare personnel providing care to the patient must appreciate the role that they play in pressure injury prevention. Materials should be prepared to meet the educational levels of different members of the interdisciplinary team [32]. Certified nursing assistants (CNAs) are an essential part of the nursing team, and their education regarding pressure injury prevention and pressure injury healing should not be neglected. Programs specifically geared towards CNAs may be developed and implemented.

NUTRITIONAL SUPPORT

Nutrition is important for maintaining skin integrity. A strong correlation exists between poor nutrition and pressure injury development [19]. Despite this fact, nutrition is often overlooked during treatment. It is of vital importance to address the nutritional needs of every individual with pressure injuries [33].

Malnutrition is defined as undernutrition or overnutrition caused by a deficit or excess of nutrients in the diet. Undernutrition occurs because intake is inadequate or the individual is unable to absorb nutrients. Overnutrition is most commonly seen in obesity. Patients with nutritional compromise should receive nutritional support, with the possible exception of patients in the end of life. Evaluation of hydration status is also an integral part of the overall nutritional picture.

Nutritional Assessment

Weight is the cornerstone in the diagnosis of malnutrition [2]. An unplanned weight loss of more than 10% in the last six months indicates a serious nutritional compromise. Signs of malnutrition include:

- Loss of subcutaneous tissue
- Muscle wasting
- Generalized edema
- Dry, pluckable hair
- Dry, flaky, itchy skin
- Cracks in the mucous membranes
- Delayed wound healing/failure to granulate

Food and fluid intake should be continuously assessed. Pay attention to food preferences and tolerances; it is beneficial to optimize the eating environment by individualizing meal times and patterns as much as possible. Culture and religion often play a significant part in food choices and attitudes toward eating. It is often necessary to consider an interdisciplinary assessment of chewing and swallowing ability and dental problems.

Malnutrition is common in elderly individuals. Older people produce less saliva, which makes swallowing more difficult. Smell and taste diminish with age, and medication can affect taste buds, causing food to become less appealing. Patients' ability to self-feed should also be monitored. The use of finger foods, adaptive utensils, and feeding assistance should be considered if necessary.

Interventions to Promote Nutrition

For patients with inadequate nutrition, strategies must be employed to increase oral intake. The preferred route of nutritional support is oral; whenever possible, the gastrointestinal tract should be used for feeding. It is the easiest and most comfortable way to provide supplementation, and it is also the least expensive and most convenient way. Patients must have diets prescribed with protein and caloric content sufficient to meet metabolic needs. The diet should consider the patient's preferences and special needs (e.g., mechanical soft diets) [4]. Daily multivitamin supplementation may need to be implemented. Mouth care should be performed prior to eating. Additionally, toileting and hand washing should be offered prior to meals.

Provide an environment conducive to eating. Position the patient properly; an upright position is preferred. Make sure the food is at the right temperature for the patient. Do not rush eating, particularly if the patient is elderly and requires more time to be oriented. Many patients benefit from the inclusion of snacks high in calories and protein in the diet (e.g., a peanut butter sandwich with milk). Consider adding powdered milk to yogurt and pudding to maximize caloric intake and protein levels. Commercial nutritional supplements, such as breakfast shakes, are also a common adjunct.

It is vital to maintain patient control as far as medically feasible. Some patients may not like ice in their water, others may prefer soup lukewarm. Patient preferences should be accommodated as much as possible.

Remind the patient to chew food thoroughly. If necessary, liquids may be offered between bites; some patients require this to help swallow their food.

Keeping patients hydrated is vitally important, and healthcare professionals should take all available opportunities to improve patients' hydration if it is medically indicated. Patients at risk of becoming dehydrated should be listed on assignment/report sheets as a reminder to monitor these patients. Fluids should be scheduled between meals at least three times a day. Patient preferences for fluids (e.g., straws, temperature, ice) should be observed and noted. Refill water pitchers frequently and keep them within reach of patients, especially those with restricted mobility. Patients should be offered something to drink at every interaction. Ambulatory patients should be provided with a water bottle. As with nutrition and positioning, it is necessary to educate patients/families about the importance of hydration. When, despite these measures, patients are unable to consume adequate levels of water or nutrients, tube feeding or parenteral feeding should be considered. Patient and family preferences and the overall goals of treatment guide these decisions [19].

EVALUATION OF THE SKIN PROGRAM

Patients at risk for skin breakdown should have a daily inspection at every interaction, including during bathing, dressing, and repositioning. Every time the patient is repositioned, the skin surfaces should be checked. This will help determine if the turning schedule is appropriate for the patient or if it should be modified. Particularly, patients should be assessed to determine if episodes of incontinence are being adequately controlled. Differential diagnosis for fecal incontinence includes infection (e.g., *Clostridium difficile*), impaction, and dietary deficits. Ongoing evaluation of interventions in use is essential to ensure that they are effective.

Assessment is a team effort and should include all members of the interdisciplinary team, including physicians, nurses and nurse assistants, physical therapists, occupational therapists, dieticians, and social workers. If an intervention is determined to be ineffective, it should be modified or changed completely. Possible modifications of a skincare plan include physical therapy to assess current level of mobility, changing seating surfaces, and correcting inappropriate body alignment when sitting.

DOCUMENTATION

Documentation of skin assessments provides information for those involved in the patient's care; it is a communication tool between the disciplines. To determine if a pressure injury is improving, documentation of the various states of the injury is necessary. This allows for evidence that the injury has improved [9]. Therefore, observations and interventions should be presented clearly and concisely. Another purpose of documentation is for a legal record of the assessment, interventions, and outcomes [7]. The individualized interventions for skin care should be documented, with specific details regarding who provided care, how often, what supplies and equipment are needed, and how the care should be undertaken. This information should be readily available to all of the patient's caretakers.

There are several tips to facilitate the complete documentation of pressure injuries. A good rule for documentation is to keep a record of the initial evaluation, interventions, patient's response, and any follow-up. All changes or complications identified should be noted. It is important to write clearly so anyone reading the chart will understand the language and the terms used.

Efforts to educate patients and/or families should be documented, including instructions given and responses from the patient/family. If a patient refuses or is unwilling to engage in certain interventions, this should become part of the documentation.

CONCLUSION

A thorough, holistic assessment of each patient at admission, with factual, concise documentation of findings, is a clear starting point for treating and/or preventing pressure injuries. Daily skin assessments for high-risk patients and informal assessment with every patient contact are recommended to ensure optimal patient care. A reliable tool, such as the Braden Scale, should be utilized to identify patients at high risk for skin breakdown, and the NPIAP guidelines should be used to stage skin breakdown appropriately. The establishment of goals consistent with the values and lifestyle of the patient and his/her family can facilitate greater patient involvement in care and adherence to prescribed interventions. A team approach in deciding appropriate individualized interventions for each patient has proven advantages. Team members should be aware of their roles in implementing the plan of care. Ongoing assessment of the interventions in place and modification/change of the plan of care as needed is the final step in implementing an individualized skincare plan. Of course, this should be supported by timely, accurate documentation.

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

Pharmacologic and Medical Advances in Obesity Management

Includes 12 Advanced Pharmacology Hours

Audience

This course is designed for all nurses, physicians, and allied professionals involved in the care of patients who are overweight or obese.

Course Objective

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.

Learning Objectives

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

1. Define obesity and related conditions.
2. Outline approaches to the clinical assessment of patients who are overweight or obese.
3. Review the epidemiology of obesity, including the evolving obesity epidemic.
4. Compare and contrast available energy expenditure research.
5. Describe the role of diet, physical activity, and body mass index (BMI) on the etiology of obesity.
6. Identify other etiologic factors contributing to the obesity epidemic.
7. Evaluate current knowledge of energy balance and defense of body weight in the regulation of body weight.
8. Define the four pillars of obesity management.
9. Analyze pharmacotherapeutic options for monogenic obesity syndromes.
10. Compare available pharmacotherapy for short- and long-term management of obesity.
11. Identify investigational antiobesity medications in development.
12. Review prescribing tips to improve the clinical use of antiobesity medications.
13. Outline available metabolic and bariatric surgical interventions, including indications, contraindications, and efficacy.
14. Discuss the role of endoscopic bariatric therapies in the management of obesity.
15. Describe the physiology and pathophysiology underlying obesity and driving advances in the management of obesity.

Faculty

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

Faculty Disclosure

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

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This activity was planned by and for the healthcare team, and learners will receive 15 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 12 pharmacotherapeutic/pharmacology contact hours.

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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

During 2017–2018 in the United States, 42.4% of adults were obese and 9.2% were severely obese [1]. By 2030, the expected prevalence will increase for both obesity (49%) and severe obesity (24%) [2].

Obesity is a chronic, progressive, relapsing, multifactorial disease involving far more than excessive fat. Obesity leads to biomechanical complications such as obstructive sleep apnea and osteoarthritis. The pathogenic adipose tissue promotes insulin resistance, metabolic syndrome, hypertension, dyslipidemia, and type 2 diabetes, progressing to cardiometabolic endpoints of nonalcoholic steatohepatitis (NASH), cardiovascular disease, and premature mortality [3].

Weight loss maintained long-term dose dependently reduces the cardiometabolic morbidity—the more weight lost, the better the outcome. This may require 16% to 20% to reduce endpoint risks, which is seldom possible with standard lifestyle intervention [4; 5; 6].

Patients may lose 5% to 10% of initial weight over 16 to 26 weeks with caloric restriction and increased physical activity, but maintaining the lost weight is very difficult because complex biological mechanisms defend the established body-fat mass [7; 8; 9]. Weight loss triggers biological pressures to regain weight through increased hunger, enhanced neural responses to food cues, heightened drive to consume energy-dense foods, and reduced metabolic rate [10; 11; 12]. Healthy diet, exercise, and behavioral interventions are crucial components of management, but seldom achieve and maintain weight loss sufficient to reduce cardiometabolic morbidities [13; 14].

However, more recent and investigational antiobesity medications show average long-term weight loss previously unattainable by nonsurgical treatment, including semaglutide (15%), combination cagrilintide/semaglutide (CagriSema) (17%), tirzepatide (21%), and retatrutide (24%) [3]. Bariatric surgery can result in dramatic weight loss (≥30%) and remission of type 2 diabetes persisting years if not decades. Minimally invasive procedures show promising results while reducing the risks of surgery. A newer treat-to-target approach with antiobesity medications uses percent weight loss as a biomarker for individualized weight reduction necessary to improve clinical outcomes [3]. Obesity requires the treatment intensity and chronicity of other complex, chronic metabolic diseases, which may involve both bariatric surgery and multi-year antiobesity medications [15].

The widely accepted causes of the obesity epidemic, increasingly sedentary lifestyles and reduced physical activity with increased fatty food intake, are largely unsupported [16; 17]. Similarly, the notion of obesity as a consequence of unhealthy personal choices reversible through diet and exercise, and other erroneous beliefs, are widely held by healthcare professionals [18].

Knowledge gaps, misperceptions and bias are highly prevalent; foremost is the failure to recognize and treat obesity as a disease [19; 20]. Among patients eligible for antiobesity pharmacotherapy and bariatric surgery, only 2% and 1%, respectively, receive the respective treatment [15; 20].

The prevalence of obesity continues increasing, but obesity medicine is in its infancy, and formal education and training in obesity care is absent from most medical curricula. Primary care practitioners are among the only providers numerous enough to address the number of patients affected. The lack of any significant education in obesity biology, prevention, or treatment in most medical/nursing schools and postgraduate training programs makes the need for continuing education that much more critical [21].

DEFINITIONS OF OBESITY

Which waist circumference parameters define central adiposity?

The World Health Organization (WHO) codified the body mass index (BMI) as a screening index for obesity in 1995. Using weight in kilograms (kg) and height in meters (m), BMI is calculated by dividing weight (kg) by height squared (m^2), or kg/m^2 [22].

In adults, population-based actuarial studies placed the upper limit of normal BMI at 25.0, defined obesity as BMI >30.0, and designated a BMI between these values as overweight. BMI categories were created, in part, to emphasize the increased mortality risk associated with a BMI both below and above the normal range (18.5–24.9). The WHO further categorized obesity severity as Class I, II, and III (***Table 1***) [7; 23]. Pediatric overweight, obesity, and severe obesity are defined by sex-specific BMI for age using the Centers for Disease Control and Prevention (CDC) growth charts [24].

Subsequent studies in Korea and Japan found higher obesity-related morbidity and mortality at BMI levels below the WHO cutoff; thus, these national guidelines defined BMI ≥23 as overweight and ≥25 as obese [22]. In addition to these specific modifications to BMI, race and cultural issues related to obesity, eating, and physical activity should be considered.

In some cases, waist circumference is more accurate in clinical diagnosis, e.g., abdominal obesity. Abdominal or central obesity is defined as waist circumference ≥102 cm (40 in) in men and ≥88 cm (35 in) in women; and among East Asians, ≥90 cm in men and ≥85 cm in women [22; 31]. These are of value only for those with a BMI between 25.5 and 34.9. It is not useful to measure waist circumference in individuals with BMI >35, as such patients are already at increased risk.

BMI DEFINITIONS OF WEIGHT			
Weight Category	**BMI Definition (kg/m²)**		
	Adult	**Adult, East Asian**	**Pediatric[a]**
Underweight	<18.5	<18.5	<5th percentile
Normal	18.5–24.9	18.5–22.9	5th–85th percentile
Overweight	25–29.9	23–24.9	≥85th percentile
Class I obesity	30–34.9	25–29.9	Obesity: ≥95th percentile
Class II obesity	35–39.9	30–34.9	
Class III obesity (severe obesity)	≥40	≥35	Severe obesity: ≥120% of the 95th percentile
[a]Based on sex-specific BMI for age			
Source: [22; 25; 26]			*Table 1*

The American Association of Clinical Endocrinology (AACE) designated obesity a chronic disease in 2012 [3; 27]. This was based on several points, including the fact that, like other chronic diseases, obesity has a complex pathophysiology involving interactions among genes, biological factors, the environment, and behavior. It meets the three criteria that constitute a disease established by the American Medical Association (AMA) [28]:

- Outward signs or symptoms: In patients with obesity, an increase in adiposity, commonly assessed via BMI, is the primary outward sign or symptom.
- Causes morbidity or mortality: Obesity is associated with multiple complications that confer morbidity and mortality.
- Involves impaired function of ≥1 tissue: Two examples of abnormal tissue function are readily identified:
  - With expansion, adipose tissue becomes inflamed and the secretion of adipocytokines is dysregulated, resulting in alterations in metabolism and vasculature and the progression of cardiometabolic disease.
  - Interactions involving satiety hormones and central nervous system (CNS) feeding centers are abnormal, resulting in increased caloric intake and body mass.

The AMA formally recognized obesity as a chronic disease in 2013 and acknowledged it had become an alarming public health threat [28].

The Obesity Medicine Association (OMA) defines obesity as a chronic, progressive, relapsing, and treatable multifactorial, neurobehavioral disease in which increased body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial outcomes [29; 30].

CLINICAL ASSESSMENT

What are considered valid measures of risk that may be used in conjunction with BMI to assess overweight and obese patients?

In 1990, the U.S. Department of Health and Human Services' Dietary Guidelines for Americans defined overweight as a BMI of at least 27 and obesity as a BMI of at least 30. Eight years later, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) released guidelines that lowered the cutoff for overweight to a BMI of 25 but maintained the definition of obesity as a BMI of at least 30 [31]. (Note: Roughly, a BMI >25 corresponds to about 10% over one's ideal weight; a BMI >30 typically is an excess of 30 pounds for most people. These are rough estimates.) The term extreme (or morbid) obesity refers to obesity with a BMI greater than or equal to 40. These final definitions are consistent with definitions used by other national and international organizations, such as the WHO. BMI does have limitations as a measurement of overweight and obesity. Although BMI provides a more accurate measure of total body fat compared with body weight alone, it can be misinterpreted in some circumstances.

Although BMI is important, there is a growing body of evidence demonstrating the impact of central adiposity on obesity-related metabolic diseases, including diabetes [32]. A study was published that compared BMI, waist circumference, and waist-to-hip ratio in predicting the development of type 2 diabetes [33]. Researchers used information collected in the Health Professionals Follow-Up Study, a prospective cohort study of 27,270 men who were followed for 13 years. During the follow-up period, 884 men developed type 2 diabetes. Waist circumference was the best predictor. Men with waists greater than 34 inches were twice as likely to develop diabetes compared to men with smaller waist sizes (i.e., <34 inches); men with waist sizes greater than or equal to 40 inches were

more than 12 times more likely to develop diabetes than men with smaller waist sizes [33]. In another study, researchers looked at waist circumference, waist-to-hip ratio, and central and subcutaneous adipose tissue measured by computed tomography (CT) as predictors of diabetes in people participating in the Diabetes Prevention Program [34]. They found that waist-to-hip ratio and waist circumference predicted diabetes; CT measurement of central adiposity also predicted diabetes but was not found to offer an important advantage over the simpler measurements. Subcutaneous adipose tissue, on the other hand, did not predict diabetes.

In 2023, the AMA adopted a policy that recognizes the issues with BMI measurement (e.g., historical harm, no consideration of gender/ethnicity) and suggests that it be used in conjunction with other valid measures of risk, including but not limited to visceral fat, body adiposity index, body composition, relative fat mass, waist circumference, and genetic or metabolic factors [35].

The AMA policy recognizes that [35]:

- BMI is significantly correlated with the amount of fat mass in the general population but loses predictability when applied on an individual level.
- Relative body shape and composition heterogeneity across race and ethnic groups, sexes, genders, and age-span are essential to consider when applying BMI as a measure of adiposity.
- BMI should not be the sole criterion used to deny appropriate insurance reimbursement.

The AMA also modified existing policy on the clinical utility of measuring BMI, body composition, adiposity, and waist circumference to support greater emphasis on education about the risk differences within and between demographic groups.

EPIDEMIOLOGY

The National Health and Nutrition Examination Survey (NHANES) is considered the authoritative source for data on obesity, diet, and related health trends [16]. NHANES is a nationally representative cross-sectional study on the health and nutritional status of noninstitutionalized U.S. civilians selected through a complex, multistage probability design. Following NHANES I (1971–1975), NHANES II (1976–1980), and NHANES III (1988–1994), biennial implementation of NHANES began in 1999 [36; 37; 38]. The U.S. Department of Agriculture (USDA) Household Food Consumption Survey (1965) and the National Health Examination Survey (NHES; 1960–1962) preceded NHANES [36].

All NHANES are conducted in-person by trained interviewers using anthropometric measurements and 24-hour dietary recall questionnaires with standardized probe questions to facilitate memory. Past-month assessment of physical activity began with NHANES III [39]. A follow-up phone interview was added in 2003 [37].

The time point used as baseline for evaluating obesity prevalence trends can importantly impact the conclusions. Because prevalence estimates can fluctuate markedly between study waves, including data from several study waves before and after the period of interest can help determine whether prevalence changes at any given time point reflect a transient anomaly or a true trend [40].

In this section, all prevalence data from 1971 to the present was obtained from NHANES except where noted. In addition, all data pertain to the United States unless otherwise mentioned.

POPULATION PREVALENCE

Adults 20 Years of Age and Older

NHES 1960–1962 included adults 18 to 79 years of age. NHANES 1971–1974 and 1976–1980 excluded individuals age older than 74 years. Therefore, ***Table 2*** is limited to adults 20 to 74 years of age for consistency in long-term trends. Prevalence rates are age-adjusted to the U.S. Census 2000 estimates. As the table demonstrates, the 1980s and 1990s mark the onset of the obesity epidemic.

Following slow increases during the 1960s and 1970s, obesity rates increased sharply through the early 2000s, modestly from 2005 to 2011, then continued climbing through 2017–2018. Male obesity surpassed female rates for the first time in 2017–2018.

Female severe obesity increased 36.4% from 1960–1962 to 1976–1980, in contrast to slowly increasing obesity and male severe obesity rates, and have exceeded male rates throughout 1960 to 2018 by a wide margin. Including ages 20 years and older lowers the 2017–2018 prevalence for obesity (42.4%) and severe obesity (9.2%), which increased approximately 39% and 96%, respectively, from 1999–2000 [1].

During 2017–2018, non-Hispanic Black Americans (49.9%) had the highest age-adjusted obesity prevalence, followed by Hispanic Americans (45.6%), non-Hispanic White Americans (41.4%), and non-Hispanic Asian Americans (16.1%), who also have lower BMI thresholds for adiposopathic (adipocyte and adipose tissue dysfunction) complications [1; 29].

The association between obesity and income or educational level is complex and differs by sex and race/ethnicity. Overall, men and women with college degrees had lower obesity prevalence compared with those with less education [43].

PREVALENCE OF OBESITY AND SEVERE OBESITY AMONG ADULTS AGED 20–74 YEARS						
Year	Percent of Population Considered Obese (BMI ≥30 kg/m^2)			Percent of Population Considered Severely Obese (BMI ≥40 kg/m^2)		
	Total	Male	Female	Total	Male	Female
1960–1962	13.4%	10.7%	15.8%	0.9%	0.3%	1.4%
1971–1974	14.5%	12.1%	16.6%	1.3%	0.6%	2.0%
1976–1980	15.0%	12.7%	17.0%	1.4%	0.4%	2.2%
1988–1994	23.2%	20.5%	25.9%	3.0%	1.8%	4.1%
1999–2000	30.9%	27.7%	34.0%	5.0%	3.3%	6.6%
2001	31.2%	28.3%	34.1%	5.4%	3.9%	6.8%
2003	32.9%	31.7%	34.0%	5.1%	3.0%	7.3%
2005	35.1%	33.8%	36.3%	6.2%	4.3%	7.9%
2007	34.3%	32.5%	36.2%	6.0%	4.4%	7.6%
2009	36.1%	35.9%	36.1%	6.6%	4.6%	8.5%
2011	35.3%	33.9%	36.6%	6.6%	4.5%	8.6%
2013	38.2%	35.5%	41.0%	8.1%	5.7%	10.5%
2015	40.0%	38.3%	41.6%	8.0%	5.9%	10.1%
2017–2018	42.8%	43.5%	42.1%	9.6%	7.3%	12.0%

Source: [41] *Table 2*

The same obesity and education pattern occurred among non-Hispanic White, non-Hispanic Black, and Hispanic women, and non-Hispanic White men, but the differences were not all significant. Among non-Hispanic Black men, obesity prevalence increased with educational attainment. No differences in obesity prevalence by education level were noted among non-Hispanic Asian women and men or Hispanic men [43].

Among men, obesity prevalence was lower in the lowest and highest income groups compared with the middle-income group. This pattern occurred among non-Hispanic White and Hispanic men. Obesity prevalence was higher in the highest income group than in the lowest income group among non-Hispanic Black men [43].

Severe obesity patterns illustrate demographic differences, by sex (women 11.5%, men 6.9%), age (40 to 59 years 11.5%, 20 to 39 years 9.1%, and ≥60 years 5.8%), and race/ethnicity (non-Hispanic Black 13.8%, non-Hispanic White 9.3%, Hispanic 7.9%, and non-Hispanic Asian 2.0%) [1].

By 2030, it is projected that 48.9% of adults will be obese, 24.2% will have severe obesity, with severe obesity projected to become the most common BMI category among women (27.6%), non-Hispanic Black adults (31.7%), and low-income adults (31.7%) [2].

Obesity prevalence studies using higher BMI cut-offs suggest a population shift toward the upper end of the BMI distribution. For example, BMI ≥35 was greater than men than women in 1959 (1%/5%), 1988–1991 (5%/9%), and 2007–2008 (11%/19%) [40].

Defining abdominal obesity as waist circumference in men (≥102 cm) and women (≥88 cm), increasing prevalence rates were found [40]:

- Overall: 52.5% in 2006–2010, compared with 36.0% in 1986–1990
- Men: 42.0% in 2009–2010, compared with 27.5% in 1986–1990 and 29.1% in 1988–1994
- Women: 61.5% in 2009–2010, compared with 44.3% in 1986–1990 and 46.0% in 1988–1994

Military-Aged Population

Obesity and physical inactivity among the military-aged U.S. civilian population (17 to 42 years of age) are considered potential national security threats because of their impact on military recruitment. Fitness eligibility for military service is defined as BMI 19.0–27.5, and adequate physical activity as ≥300 minutes per week of moderate-intensity aerobic physical activity [44].

PREVALENCE OF OBESITY AND SEVERE OBESITY AMONG THOSE 2 TO 19 YEARS OF AGE						
Year	**Obese**			**Severely Obese**		
	Total	**Boys**	**Girls**	**Total**	**Boys**	**Girls**
1966–1970	4.6%[a]	N/A	N/A	N/A	N/A	N/A
1971–1974	5.2%	5.3%	5.1%	1.0%	1.0%	1.0%
1976–1980	5.5%	5.4%	5.6%	1.3%	1.2%	1.3%
1988–1994	10.0%	10.2%	9.8%	2.6%	2.7%	2.6%
1999–2000	13.9%	14.0%	13.8%	3.6%	3.7%	3.6%
2001	15.4%	16.4%	14.3%	5.2%	5.1%	4.2%
2003	17.1%	18.2%	16.0%	5.1%	5.4%	4.7%
2005	15.4%	15.9%	14.9%	4.7%	4.9%	4.5%
2007	16.8%	17.7%	15.9%	4.9%	5.5%	4.3%
2009	16.9%	18.6%	15.0%	5.6%	6.4%	4.7%
2011	16.9%	16.7%	17.2%	5.6%	5.7%	5.5%
2013	17.2%	17.2%	17.1%	6.0%	5.6%	6.3%
2015	18.5%	19.1%	17.8%	5.6%	6.3%	4.9%
2017–2018	19.3%	20.5%	18.0%	6.1%	6.9%	5.2%

N/A = not available.
[a]Ages 12 to 17 years only

Source: [42] *Table 3*

Among military-aged participants in the 2015–2020 NHANES, only 34.3% were BMI- and activity-eligible. The prevalence of eligible and active status was higher among men, persons who were younger and non-Hispanic White, college graduates, and those with higher family income than among their counterparts [44].

The BMI-ineligibility in this study exceeds those in previous studies. This upward trend in military ineligibility mirrors the increase in population prevalence of obesity. This study also draws attention to the military preparedness repercussions of the inequitable distribution of unhealthy weight and inadequate physical activity [44].

Pediatric Population

Although adult obesity is the focus of this course, long-term population trends in pediatric obesity (age 2 to 19 years) provide an informative companion to adult trends. In ***Table 3***, note that pediatric obesity increased >300% from 1976–1980 to 2003, but only 11.4% from 2003 to 2017–2018. Compared with adult obesity, pediatric obesity shows a smaller relative increase over the past 20 years, and pediatric severe obesity has consistently greater prevalence in boys.

INCIDENCE

Using the nationally representative Panel Study of Income Dynamics (PSID), the incidence of new obesity cases (i.e., the first time a person has a BMI ≥30) was examined from 2001 to 2017 among 13,888 adults ≥20 years of age [45]. Obesity incidence, stable over 2001–2005 to 2009–2013, increased 18% in 2013–2017 to 40.7 per 1,000 person-years. This means that, on average, 4% of the adult population entered obese BMI each year during 2013–2017 (***Table 4***). This is similar to obesity prevalence, which began rising notably after 2011 following modest increase from 2005 to 2011.

During 2001–2017, Black individuals had higher obesity incidence than White individuals, which was particularly high in Black women (57.9 per 1,000 person-years) and Black young adults 20 to 29 years of age (65.5 per 1,000 person-years). Over the study period, the relative difference in obesity risk between Black and White persons decreased from 92% to 43%, but large race disparities remained in 2013–2017, consistent with obesity prevalence data.

PREVALENCE OF OBESITY AND SEVERE OBESITY AMONG THOSE 2 TO 19 YEARS OF AGE					
Group	Incidence per 1,000 Person-Years				
	2001–2005	2005–2009	2009–2013	2013–2017	Total (2001–2017)
Overall	34.1	36.4	34.5	40.7	28.1
Female	30.9	35.6	33.7	38.1	26.5
Male	37.6	37.1	35.6	44.0	30.2
White	31.6	33.8	32.0	39.1	26.2
Black	60.3	62.0	61.4	57.9	47.9
Less than high school	44.8	55.8	46.1	50.3	39.4
High school diploma	38.1	45.1	45.8	50.1	34.5
More than high school	30.6	30.9	28.7	36.8	24.7
Source: [45]					*Table 4*

By educational level, the incidence of obesity increased most for those who had a high school diploma (32% increase) followed by those with an education beyond high school (20%), whereas it remained roughly the same for those with less than a high school diploma. Those with less than high-school education had higher obesity incidence than those with education beyond high-school (39.4 per 1,000 person-years vs 24.7 per 1,000 person-years) [45].

By age, obesity incidence was highest in young adults (34.1 per 1,000 person-years) and declined with age (70+ years: 18.9 per 1,000 person-years). As obesity prevalence climbs, the pool of never-obese adults who may develop first-time obesity becomes smaller, which partly explains the higher incidence at younger ages [45].

With the obesity risk of overweight persons seven times higher than normal-weight persons (62.1 per 1,000 person-years vs 8.8 per 1,000 person-years), the authors state overweight should not be considered a "new normal," but a transition phase that often cascades into obesity. The obesity incidence of young adults with overweight (97.0 per 1,000 person-years) was the highest of any subgroup examined [45].

PERSONAL AND SOCIETAL BURDEN OF OBESITY

A 5-point increase in BMI is strongly associated with increased risk for which cancers?

As noted, obesity is a progressive, chronic disease associated with a spectrum of complications and poor outcomes, including premature death [46]. Common clinical consequences of obesity are adiposopathic or metabolic (e.g., type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, cancer) and biomechanical stress damage from the pathogenic physical forces of excessive body fat (e.g., orthopedic abnormalities leading to immobility, sleep apnea) [29; 46]. Obesity shares many pathogenic processes of aging. The greater the age or obesity, the greater the mortality. In patients with BMI 55–60, an estimated 14 years of life is lost primarily from heart disease, cancer, and type 2 diabetes [18].

Excessive body fat is a cause of 13 cancers, including esophageal, gastric, cardiac, colorectal, liver, gallbladder, pancreas, meningioma, postmenopausal breast, endometrium, ovary, kidney, thyroid, and multiple myeloma [47]. A 5-point increase in BMI is strongly associated with increased risk of thyroid and colon cancers in men, endometrial and gallbladder cancers in women, and esophageal adenocarcinoma and renal cancers in both sexes [46]. From 2004 to 2015, the prevalence of these cancers increased 7% while cancers not known to be related to excessive body fat decreased 13% [46]. Overweight- and obesity-related cancers account for about 40% of all cancers. With approximately 70% of adults overweight or obese, promoting the maintenance of weight loss to decrease cancer risk is critical [47].

Obesity is also associated with increased susceptibility to nosocomial infections, wound infections, and influenza pandemics. Obesity increased the risk of COVID-19-related hospitalization (113%), intensive care admission (74%), and death (48%) [48].

Previously associated with high-income Western countries, obesity has become a growing problem in developing countries and among low-income populations. For the first time in human history, the number of overweight people exceeds the number of underweight people. Globally, the estimated $2.0 trillion annual economic impact of obesity is similar to smoking ($2.1 trillion), or armed violence, war, and terrorism combined ($2.1 trillion) [49].

ALL-CAUSE MORTALITY BY BMI		
Weight Category	**BMI**	**Hazard Ratio**
Underweight	**15.0–18.4**	**1.51**
Healthy or normal	18.5–19.9	1.13
	20.0–22.4	1.00
	22.5–24.9	1.00
Overweight	25.0–27.4	1.07
	27.5–29.9	1.20
Class I obesity	30.0–34.9	1.45
Class II obesity	35.0–39.9	1.94
Class III obesity	≥40	2.76
Source: [53]		*Table 5*

In the United States, medical expenditures by BMI show a J-shaped curve, with higher costs in general for women and the lowest expenditures at a BMI of 20.5 for women and 23.5 for men. Among persons with BMI greater than 30, predicted costs continued to increase linearly, with each one-unit increase in BMI associated with an additional cost of $253 per person on average [2]. In 2019, the medical cost of adult obesity was $173 billion, with most costs from severe obesity; pediatric obesity was associated with medical costs of $1.32 billion. Adults with BMI 20–24 had the lowest medical costs in all ages [50].

Obesity-related costs increase with age starting around 30 years of age. This is similar to findings of increased relative risks of obesity-related morbidity and mortality starting at 25 to 29 years of age and 35 years of age and older, respectively. The high costs at higher levels of BMI are especially concerning given that the adult prevalence of severe obesity is projected to increase further [50].

MORTALITY

In 2013, an influential meta-analysis by Flegel et al. concluded that, relative to normal weight, class 1 obesity (BMI 30.0–34.9) was not associated with excess all-cause mortality and overweight was associated with lower all-cause mortality [51]. The hypothetically protective metabolic effects of increased body fat in apparently healthy individuals was advanced to support this claim [52].

However, uncontrolled variables may have biased the results. A subsequent meta-analysis of 239 prospective studies on BMI and mortality limited bias from confounding factors and reverse causality. Of 10.6 million participants in North America, Europe, Australia and New Zealand, and Asia, analyses was restricted to 3.9 million never-smokers without specific chronic diseases at enrollment who were still followed after five years (median follow-up: 13.7 years). The six WHO-defined BMI categories were subdivided into nine BMI groups to avoid merging importantly different risks [53].

All-cause mortality (***Table 5***), lowest at BMI 20–24.9, increased significantly with greater distance below and above this range, (e.g., 51% for BMI <18.5 and 276% for BMI ≥40 compared with BMI 20–24.9). Each 5-point increase in BMI above 25.0 increased the risk of all-cause mortality by 39% in Europe and east Asia, 31% in Australia/New Zealand, and 29% in North America, and was greater in younger than older people (52% at 35 to 49 years of age; 21% at 70 to 89 years of age) and in men than women (51% vs 30%). The hazard ratio for class 1 obesity in men (1.70) and women (1.37) suggests that men have almost double the proportional excess mortality of women (70% vs 37%).

The proportion of all-cause mortality attributable to overweight or obesity was 19% in North America, 16% in Australia/New Zealand, 14% in Europe, and 5% in east Asia [53].

The results challenge assertions that overweight and class I obesity are not associated with higher mortality risk. The results section in this paper also reproduced the findings of Flegal et al., before applying restrictions that yielded the final results [53]. The results also suggest a J-shaped curve for mortality risk below and above BMI 20–25, which includes normal-range BMI 18.5–20.

ETIOLOGY OF THE OBESITY EPIDEMIC

The development of obesity is commonly understood through the energy balance model. Energy refers calories from macronutrients (carbohydrate, protein, and fat) in meals. Energy (i.e., calories) can be ingested (intake) or burned (expenditure). Energy balance is when energy intake and expenditure are equal. In positive energy balance, energy intake exceeds expenditure. Long-term positive energy balance is considered the cause of adult obesity. Obesity, both societal and individual, is abundantly blamed on increasingly sedentary lifestyles and reduced physical activity, combined with increased fatty food intake.

Utilizing the NHANES and International Atomic Energy Agency (IAEA) databases, researchers have investigated population-level trends that may be affecting energy balance, including changes in diet, activity, and energy expenditure. The results challenge conventional wisdom about the causation of the obesity epidemic. These data are limited to U.S. adults.

DIET, PHYSICAL ACTIVITY, AND BMI

Dietary recommendations represent an important but neglected backdrop of population trends in weight-gain over the past 70 years. In the 1950s, the Diet-Heart Hypothesis (DHH) connected rising rates of coronary heart disease after World War II to high saturated fat intake: Because dietary saturated fat raises serum cholesterol and high cholesterol contributes to coronary heart disease, then saturated fat intake must also cause coronary heart disease [54]. The American Heart Association (AHA) promulgated the DHH and advocated reducing total fat consumption to 25% to 35% of calories and substituting polyunsaturated for saturated fatty acids to palliate high cholesterol in 1961 [55; 56; 57].

With little data to support the AHA's recommendation, the Minnesota Coronary Experiment (MCE) (1968–1973) was expected to provide definitive evidence. Ancel Keys, the co-investigator, had invented K-rations for the U.S. Army in WWII, devised the DHH and was also President of AHA. This double-blind randomized controlled trial, the largest and perhaps the most rigorously executed trial ever conducted on dietary change and mortality, included complete postmortem assessments. Replacement of saturated fatty acids with polyunsaturated fatty acids predictably lowered serum cholesterol. Paradoxically, MCE participants with greater reductions in cholesterol had higher mortality. The results of what would have been a landmark study remained unpublished for 43 years, until 2016 [58].

During this time, Congress formalized AHA's position and the DHH with the *Dietary Guidelines for Americans*, introduced in 1980 and updated every five years. The Surgeon General, National Research Council, and American Cancer Society also recommended low-fat/saturated fatty acid diets to reduce coronary heart disease and cancer. The *Dietary Guidelines for Americans* was pivotal in linking saturated fatty acids as a major cause of heart disease, obesity, and cancer, yet was initially opposed by some experts over potential unintended consequences, lack of evidence that lower dietary fat reduced heart disease, and evidence implicated sugar and refined carbohydrates instead of fats [57; 59; 60].

The 1980s *Dietary Guidelines for Americans* recommended reducing all fats and increasing carbohydrates to 55% of total calories, which was also proposed to help prevent overweight and obesity [36]. In 1990, total fat was capped at 30% of calories, later revised to 20% to 35%, which remained until 2010 [60]. Federal agencies and medical associations strongly supported a low-fat/saturated fatty acid, high-carbohydrate diet for everyone older than 2 years of age, and through 2008, advocated sugar as healthy for persons with diabetics and the general population [61]. The belief that dietary fat drives obesity and heart disease persists [1].

Macronutrient Intake and BMI: 1965–2011

Changes in macronutrient proportion of average daily calories and BMI have been examined in the context of dietary recommendations [36]. U.S. adults have largely followed dietary guidelines. From 1965 to 1999, total calories from fat decreased (46% to 32%) while carbohydrates concurrently increased (39% to 52%) [36]. From 1965 to 2011, the increased caloric share from carbohydrate explained 85% of increased BMI in men and 91% in women. Increases in total caloric intake since 1971 were unlikely to explain the increase in BMI [36]. In other words, increased carbohydrate proportionality, not total calories, drove rising BMI.

As discussed, the onset of rising obesity occurred during the 1980s and 1990s as the DHH became an ideology propagated by federal government dietary recommendations, public health policies, and popular health media, which these authors suggest may have initiated the obesity epidemic [36; 54; 63]. While observational data cannot establish causality, these and other findings suggest the origin of the obesity epidemic may be partially iatrogenic.

Dietary Changes: 1999–2016

From 1999 to 2016, data showed increases in total fat (1.2%) as proportion of diet, including saturated (0.36%), monounsaturated (0.19%), and polyunsaturated (0.65%) fatty acids; decreases in total (-2.02%) and low-quality (mostly sugar) (-3.25%) carbohydrates; increases in high-quality (1.23%) carbohydrates; and increased intake of whole grains, poultry, and nuts [37].

Opposing trends during 1999–2016 partly reversed those of 1971–2000, when emphasis on low-fat diets was associated with decreased fat intake and increased refined grains and added sugar intake. During the 2000s, the benefits of healthy fats and plant sources of protein and harms of excess sugar became popularized, independent of dietary guidelines. Regardless of influence, dietary macronutrient intake during 1999–2016 shows clear evidence of improvement [37].

Caloric Intake, Physical Activity, and BMI: 1971–2008

Changes in physical activity, macronutrient intake, and BMI during 1971 to 2008 were examined using NHANES dietary (1971–2008) and physical activity (1988–2006) data of participants with BMI 18.5–50.0. Physical activity was defined as the weekly frequency of leisure time activities of moderate or greater metabolic intensity [39].

Between 1971 and 2008, BMI increased 10% in men and 11% in women, most of which occurred after 1988 [39]. Total calories per day increased by approximately 10% in men and 14% in women from 1971 to 1999, peaked in 2003, and declined to 1999 levels for both sexes by 2008. Relative caloric intake (i.e., total calories converted to cal/kg of body weight) in 2008 was similar to 1971 but increased modestly between 1988 and 1994 in both sexes. Percent of daily calories (men and women) increased for carbohydrate (13% and 10%) but decreased for fat (9% and 8%) and protein (5% and 7%) [39].

Between 1988 and 2006, physical activity per week increased 47% in men and 120% in women [39]. Adjusted for physical activity and carbohydrate and fat intake, for an equivalent amount of energy intake or physical activity, BMI was up to 2.3 higher in 2006 than in 1988. Thus, BMI increased between 1988 and 2006, even after holding energy intake, macronutrient intake, and physical activity constant.

Decreased physical activity and increased caloric consumption do not fully explain this increase in BMI. The authors conclude that other unrecognized factors may be significantly modifying how energy intake and expenditure influence body weight over time [39].

Weight Loss Attempts: 1999–2016

Over the past 40 years, as obesity prevalence increased about threefold, the prevalence of weight loss attempts by adults increased from 34% in 1999–2000 to 42% in 2015–2016. During 2013–2016, past-12-month attempts to lose weight were made by 49% of adults overall and by 67% of those with obesity. Since the late 1980s, the prevalence of dieting to lose weight has been ≥40% among women and ≥25% among men [64; 65].

Repeated weight loss efforts may also contribute to weight gain, which experts have suggested has created a "weight-loss futility cycle" that characterizes the rising prevalence of both obesity and weight loss attempts since 1980. The increasing prevalence of obesity and weight loss attempts has also been paralleled by an increase in body weight stigma, which in turn is associated with many adverse health outcomes, including higher risk of all-cause mortality, and disproportionately affects individuals with obesity [65].

ENERGY EXPENDITURE RESEARCH

What is basal energy expenditure?

Understanding the relative contribution of lower energy expenditure to the obesity epidemic is a crucial task that requires accurate measurements of energy expenditure [66; 67; 68]. The terms used in discussions of this concept should be clearly defined [70; 71; 72]:

- Basal energy expenditure: Also known as resting energy expenditure or basal metabolic rate, the minimum energy required to maintain vital physiological functions
- Activity energy expenditure: Exercise and non-exercise activity
- Physical activity: Work-time (occupational) or leisure-time energy expenditure
- Total energy expenditure: Expressed in calories/day, the sum of basal energy expenditure and activity energy expenditure

Doubly labelled water (DLW) is the criterion-standard for measuring energy expenditure and the only method that can assess this during a person's normal daily living. This method uses water with the added stable isotopes deuterium and oxygen-18 to measure energy expenditure (i.e., calories burned) [67; 73].

DLW studies began in the early 1980s. The IAEA database houses four decades of DLW study data. With the size of this database and its ongoing expansion, big questions about the causes of the obesity epidemic are being addressed [74].

Additive versus Constrained Models of Metabolic Physiology

The dominant additive model assumes a dose-dependent, additive effect of physical activity on total energy expenditure; with each increment of physical activity, total calories burned correspondingly increases [75]. This calories in/calories out paradigm of obesity led to energy restriction diets and exercise as the standard obesity intervention to reverse positive energy balance for weight loss [76; 77].

Energy compensation, or metabolic adaptation, is a normal physiobehavioral response to a change in activity or diet such that the impact of the change is blunted [12]. DLW data suggest the relationship between physical activity and total energy expenditure is more complex than additive models allow [75].

An earlier DLW study involved Hadza people, traditional hunter-gatherers who live off of wild plants and animals in Tanzania expending hundreds of calories a day on activity. Hadza men ate and burned about 2,600 calories per day and Hadza women consumed and burned about 1,900 calories per day. Even after controlling for effects of body size, fat percentage, age, and sex, the Hadza burned about the same daily calories as city dwellers in the United States [78].

DLW evidence led to the constrained model, where total energy expenditure increases with low physical activity but plateaus at higher activity levels as the body adapts to maintain total energy expenditure within a narrow range. By accounting for energy compensation, the constrained model provides a unifying framework for seemingly contradictory results from studies of physical activity and total energy expenditure [12; 75].

The compensation may take several weeks or months. Exercise will raise energy expenditure in the short-term, and lifestyle change may also affect total energy expenditure until compensation occurs, after which physical activity will have little measurable effect on total energy expenditure [12].

Energy Compensation

Increasing activity levels may bring diminishing returns due to compensatory responses in nonactivity energy expenditure [66]. In 1,754 adults with DLW measured seven years apart, only 72% of the extra calories burned during activity translated into extra calories expended that day, because the body offset the calories burned in activities by 28%. Among those with BMI ≥34, compensation of burned activity calories increased to 46% [72].

To explain the causality of this relationship, individuals with greater body fat are either predisposed to adiposity because they are stronger energy compensators or because they become stronger compensators as they gain adiposity. Prescribing increases in activity to increase total energy expenditure and thus control weight gain or promote fat loss assumes that costs of activity are additively related to basal costs, which this study suggests is untrue [72].

Resting Energy Expenditure in Healthy Underweight Adults

Contrary to popular belief that lean individuals "eat what they want" and exercise more, a cohort of 150 healthy underweight (BMI <18.5) adults exhibited significantly lower physical activity and food intake relative to 173 normal-BMI controls and much higher than expected resting energy expenditure, measured using DLW [79]. The healthy underweight subjects were metabolically healthier than normal-BMI controls, which suggests low body weight/fat is a more potent driver of metabolic health than higher physical activity. The results extend previous longitudinal findings into a much lower range of BMI and show that markers of metabolic health continue to improve as BMI falls below 18.5 [79].

Declining Metabolic Rate and Rising Obesity

The obesity epidemic is often blamed on declining energy expenditure due to reduced occupational physical activity combined with increased sedentary behavior and screentime. This was examined in 4,800 adults with DLW data obtained between 1987 and 2017. All results were adjusted for age and body composition [80].

Men and women both showed significant declines in total energy expenditure and significantly increased activity energy expenditure, while physical activity increased significantly in men and non-significantly in women. Basal energy expenditure decreased significantly in men and non-significantly in women. Men and women showed declines in total energy expenditure (7.7% and 5.6%) and basal energy expenditure (14.7% and 2%), respectively. In both sexes, the decline in basal energy expenditure was sufficient to explain the reduction in total energy expenditure. There was no evidence that reduced physical activity leading to lowered total energy expenditure contributed to the obesity epidemic [80]. This is counterintuitive, given the established decrease in occupational physical activity and the suggested progressive increase in sedentary behavior. The increased leisure physical activity between 1965 and 1995 (and 1988–2006) may have offset reduced occupational physical activity. Increased time on computers has largely come at the expense of time watching television; with comparable energy costs, this tradeoff would have little effect on overall activity energy expenditure [80; 81].

In addition, the reduction in total energy expenditure was linked to a decline in basal energy expenditure. Declining basal energy expenditure is less easily understood, but consistent with data that body temperatures also declined over the same period as decreasing basal metabolic rate. The magnitude of change in basal metabolic rate is consistent with studies showing that basal metabolic rate increases 10% to 25% with every 1°C increase in core temperature [80]. The authors conclude that a declining basal metabolic rate may be contributing to the obesity epidemic. Identifying the cause, and if it can be reversed, is an urgent priority.

OTHER POTENTIAL ETIOLOGICAL FACTORS

Urbanization

During 1985 to 2014 in most countries, the concurrent increases in BMI and the proportion of populations living in cities compared with rural areas led to a widely accepted view that urbanization, and the resultant sedentary lifestyle, is an important contributor to the global rise in obesity [82]. However, an analysis of 2,009 population studies with direct anthropometric measurements in 112 million adults from 1985 to 2017 demonstrated that 55% of the global rise in adiposity (and >80% in some low- and middle-income regions) is explained by increased adiposity in rural areas [83].

Social Contagion

What is the role of social contagion on obesity rates?

There is substantial clustering of obesity within social and geographic networks. Whether this results from causal pathways (e.g., social contagion, shared environments) or self-selection is unclear and was studied in 1,519 military families from 38 military installations around the United States who relocated to counties with obesity rates of 21% to 38% [84]. Exposure to communities with higher obesity prevalence was associated with higher BMI and overweight/obesity in parents and children. Specifically, a 1% higher county obesity rate was associated with 5% higher odds of obesity in parents and 4% higher odds of overweight/obesity in children [84].

All associations were strengthened by duration (i.e., >24 months at their current installation) and proximity (living off-base) of exposure and were unchanged after controlling for the shared built environment in the county and neighborhood of residence. There was no evidence to support self-selection or shared environment as explanations, which may suggest the presence of social contagion in obesity [84]. Although data on the previous county obesity rate was unavailable, exposure to communities with higher obesity rates may increase individuals' BMI via the presence of social contagion, possibly by common social norms associated with obesity [85].

Medication-Induced Weight Gain

In 2017–2018, 20.3% of U.S. adults used an obesogenic medication (compared with 13.2% in 1999–2000) [86]. Many widely used drugs cause weight gain that may lead to obesity in susceptible individuals. Weight gain is consistently associated with many older antidiabetic agents, atypical antipsychotics, antidepressants, and antiepileptic drugs [87].

Dietary Sugar and Sugar-Sweetened Beverages

A study that pooled three population-based prospective cohorts of Finnish adults to examine diet and weight gain over seven years found no associations between total carbohydrate, dietary fiber, sugar, or sucrose intake and ≥5% increase in weight or waist circumference. However, the authors state that low sugar-sweetened beverage consumption in Finland compared with the United States may partially explain the lack of association between carbohydrate intake and weight gain [88].

In the United States from 1965 to 2002, daily sugar-sweetened beverage caloric consumption increased 306% per capita and 86% among consumers of sugar-sweetened beverages only. However, from 1999 to 2010, total daily caloric intake from sugar-sweetened beverages among youth (2 to 19 years of age) and adults (≥20 years of age) decreased 31% and 21%, respectively [57].

Evidence for the mainstream view that high sugar consumption leads to obesity and related metabolic diseases is inconsistent, and high sugar intake from sugar-sweetened beverages may differ from sugar-containing foods (i.e., solid sugars) in BMI/metabolic impact [89].

In a review of prospective evidence, most studies linking high sugar intake to adverse health outcomes examined sugar-sweetened beverages, while studies of solid sugar intake mostly reported null findings. High sugar-sweetened beverage consumption was dose dependently associated with increased risks of cardiovascular disease morbidity and mortality through weight gain; solid sugar sources (e.g., ice cream) were not [89; 90].

Sugar-sweetened beverages may be more likely to induce metabolic syndrome. The faster gastric emptying time of sugar-sweetened beverages and higher absorption of its fructose component may lead to fatty accumulation in the liver. Compared with solid sugars, sugar-sweetened beverages induce less satiety and may subsequent cause overeating. The gut can convert low-concentration fructose to glucose, but transports high-concentration fructose (e.g., in sugar-sweetened beverages) to the liver [89].

Increased lipogenesis and circulating triglycerides, very-low-density cholesterol, and uric acid associated with high sugar-sweetened beverage intake may induce hyperglycemia, glucose intolerance and dyslipidemia to increase risks of type 2 diabetes and cardiovascular disease. High intake of fructose-sweetened beverages may disrupt the production of appetite control hormones (decreasing leptin and insulin, increasing ghrelin), suggesting different effects on metabolic and endocrine health of liquid versus solid sugars [89].

Individuals who ingest high dietary sugar often have other unhealthy behaviors that may contribute to the pathogenesis of obesity and related disorders, complicating causal inferences. Although definitive evidence is needed, and reducing sugar remains a general recommendation, there is evidence of greater health risks with sugar-sweetened beverages that might not be comparable to those with sugar in food [89; 91].

SUMMARY

What is known about the role of endocrine-disrupting chemicals on body weight?

That the obesity epidemic lacks a clear explanation is a striking and poorly appreciated fact. The widely accepted causes of ever-increasing caloric intake and progressively declining physical activity are largely unsupported [16; 17]. Genetic, developmental, and environmental factors are thought to interact to cause cumulative positive energy balances resulting in weight gain and obesity [92]. Numerous factors have been

associated with increased risk of obesity—but a risk factor is not necessarily a cause, and risk factors are not direct causes of disease. Associations in the obesity literature often reflect information bias, reverse causality, erroneous causal inferences, or confounding from other social and behavioral factors [54]. Although spurious, some persist to mislead science, practice, and the public [59].

Provocative evidence demonstrates that the obesity epidemic has expanded beyond humans. Mammals inhabiting human-influenced environments have also exhibited pronounced increases in weight and obesity over the past several decades, including mammals in research labs, feral rats, and domestic dogs and cats [93]. The laboratory animals include four different species of primates in National Primate Research Centers, as well as rats and mice, all living in environments where their diets are strictly controlled [17; 93]. In 2015, canine and feline obesity rates had reached pandemic proportions similar to humans [94]. An international multidisciplinary congress, Animal Obesity, was launched in 2016 [95].

A reasonable inference is that something has changed in the shared environment that is inducing weight gain, and exposure to unidentified obesity-promoting factors may be affecting all these populations in concert. There is some evidence pointing to endocrine-disrupting chemicals [17; 48; 77; 93; 96].

Endocrine-disrupting chemicals interfere with hormone action to dysregulate endocrine function, insulin signaling, and/or adipocyte function. Adipose tissue is a true endocrine organ and is therefore highly susceptible to disturbance by endocrine-disrupting chemicals. Obesogenic endocrine-disrupting chemicals promote adiposity by altering programming of fat cell development, increasing energy storage in fat tissue, and interfering with neuroendocrine control of appetite and satiety [17; 18; 48; 77; 96; 97].

Endocrine-disrupting chemicals have become ubiquitous in our environment. Exposure occurs throughout life, but development is the most sensitive period for endocrine-disrupting chemicals to impact future weight gain across the lifespan and generations, and endocrine-disrupting chemicals can act via epigenetic mechanisms. There is an urgent need to understand how exposures to certain endocrine-disrupting chemicals may predispose the population to obesity [48; 77; 96; 98; 99].

Note that researchers in some studies have concluded that some unknown factor may be altering normal energy metabolism, as increased caloric intake and/or decreased activity could not adequately explain rising BMI and obesity. A 2023 review suggests that exposure to some yet-to-be-identified factor(s) is promoting obesity by generating false and misleading information about energy status [100].

Most importantly, uncertainty over the obesity epidemic's cause has little bearing on the effectiveness of medical interventions [16]. In fact, pharmacotherapy of obesity with novel approved and investigational agents shows weight loss efficacy and remission of comorbid disorders previously unattainable without bariatric surgery. Bariatric surgery itself can result in dramatic weight loss (≥30%) and remission of obesity-related metabolic disorders persisting for years if not decades. Newer and emerging minimally invasive bariatric procedures are showing promising results while reducing the risks of surgery.

THE REGULATION OF BODY WEIGHT

ENERGY BALANCE

When body-fat levels become established, complex biological mechanisms defend the established body mass against persistent pressures that would induce weight loss. This can be understood from an evolutionary perspective. With food scarcity during most of human evolution, evolutionary pressures on the human genetic blueprint selected for genetic variants that favored the storage and conservation of energy to ensure survival and reproduction. The underlying process that defends energy storage and conservation is called energy balance [101; 102].

The purpose of energy balance is to maintain adenosine triphosphate (ATP) availability for cells. ATP is required by all cells to sustain and maintain life. Eating acquires the oxidizable fuels that cells use to maintain ATP availability [101; 102; 103].

Energy balance is regulated by homeostatic processes. Homeostasis maintains interdependent bodily constituents within a controlled stable range. Regulation is the ability to maintain a variable within a narrow range. Control mechanisms are those that maintain the narrow range of the regulated variable. The regulated variable in energy homeostasis is ATP availability [103; 104]. Control processes that maintain ATP availability (i.e., energy homeostasis) include energy intake, energy storage, and energy expenditure. Thus, ATP availability is the apex regulated variable and pivot point for energy balance; the dynamic relationships between energy intake, storage, and expenditure are all directed toward this end [103].

Energy Intake and Storage

Glucose and free fatty acids are monomers, the oxidizable fuels for ATP production that cells require. Monomers are the breakdown products of macronutrients, released by digestion and distributed into oxidizable fuels or storage by energy partitioning, depending on current energy balance status [70; 102; 103].

Excess energy is stored as fat in adipose depots, carbohydrate (as glycogen) in liver, or protein in muscle. The energy density of adipose tissue is nearly 10-fold greater than liver (glycogen) or muscle (protein). The small storage capacity for carbohydrate can cover overnight energy needs during sleep. The larger energy stores of fat are mobilized to cover longer-term energy shortages [70; 102; 103].

However, as a substrate for energy metabolism, fat is last in the hierarchy that determines fuel selection; it is mostly stored before oxidation and is less likely to be oxidized than carbohydrate or protein. Body-fat mass and oxidation of dietary fat are inversely related—higher fat mass lowers the oxidation rate of dietary fat [70; 102; 103]. Energy expenditure is the sum of ATP generated by oxidizing monomers to drive physiological processes.

Three States of Energy Balance

Oxidizable fuels from food can fail to meet (negative), equal (balanced), or exceed (positive) requirements to maintain ATP availability within its narrow range. These are the three states of energy balance [70; 102; 103]:

- Negative: When oxidizable fuel supplies are challenged by prolonged calorie deficit, control mechanisms increase catabolism (breakdown) of fuel stores and reduce energy expenditure to maintain ATP production. During starvation, these mechanisms maintain cell function to an extent that compromises organ and systemic function. The collective outcome of processes that control blood glucose, adiposity, heat production, and eating behaviors, are directed toward maintaining ATP availability within a narrow range.
- Balanced: The rate of anabolic and catabolic processes is equal (a state of energy balance).
- Positive: Energy balance favors anabolism, which increases fuel stores.

Unlike fuels, ATP cannot be stored. An animal can survive for days or weeks without food, but its survival time is measured in seconds if a toxin shuts down oxidative phosphorylation and ATP production. Lacking ATP storage capacity, daily ATP turnover in humans is dramatic [103].

DEFENSE OF BODY WEIGHT

The biological pressure to gain weight is a consequence of what factors?

Positive energy balance from increased energy intake, decreased energy expenditure, or both, is considered the proximate cause of weight gain and excess fat storage leading to obesity [66; 102; 105; 106; 107].

Obesity is usually the result of small, cumulative positive energy imbalances over an extended period. The homeostatic system continually retunes itself during the upward drift in weight. At some point, for most people, these biological adaptations re-establish a balance at a higher, steady-state weight [108].

Persons with obesity may lose 7% to 10% of initial weight with a 16- to 26-week comprehensive caloric restriction, physical activity, and behavioral intervention [9]. However, it is the maintenance of weight loss that makes long-term control of obesity so difficult [7; 8].

In contrast to its subtle, permissive role in the development of obesity, biology plays a prominent, causal role in weight regain [108]. Energy-restricted weight loss mobilizes powerful biological forces that lead to increased hunger, enhanced neural responses to food cues, and heightened drive to consume energy-dense foods [11].

Because both sides of the energy balance equation are affected after weight loss, the biological pressure to gain weight is a consequence of both increased appetite and suppressed energy expenditure as the body attempts to restore energy homeostasis [15; 108]. Termed metabolic adaptation, this defense of established adiposity against weight loss recapitulates a physiological response that signals potential starvation [69; 104].

Metabolic adaptation has been understood for more than five decades but is missing in public health statements that healthier lifestyle choices are the solution to obesity [6; 109; 110; 111; 112; 113; 114]. As a consequence, patients are often blamed for obesity treatment failure [3; 6].

OVERVIEW OF CLINICAL MANAGEMENT

Obesity involves dysfunction of the tightly regulated energy homeostasis system and its underlying central, peripheral, and reward mechanisms (***Appendix***) [115; 116]. Powerful compensatory mechanisms drive weight regain following weight loss in obesity by altering appetite, food reward, and energy intake and expenditure. Peripheral changes, including reduced anorectic hormones and increased orexigenic hormones, stimulate food intake. Pressure to overeat combines with central mechanisms that drive food pleasure and reward. Metabolic adaptation reduces resting energy expenditure [117]. These dysregulated mechanisms are the targets of FDA-approved and investigational antiobesity medications and of bariatric surgery.

Knowledge of obesity pathophysiology, and clinical management based on the understanding of obesity as a chronic, progressive cardiometabolic disease, has rapidly evolved over the past decade. Consequently, some clinical practice guidelines on obesity from authoritative bodies have become outdated. For example, the most recent guideline by the AHA, Ameri-

can College of Cardiology, and The Obesity Society (AHA/ACC/TOS) was published in 2014 [118]. The paradigm of long-term management in this guideline is largely obsolete. A 2015 clinical practice guideline from the Endocrine Society and a 2016 guideline from the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) advanced the paradigm to the current standard of care, but available antiobesity medication options addressed in the guideline are non-recent [119; 120; 121]. Scientific statements by the Endocrine Society and clinical practice guidelines by the OMA, the American Gastroenterological Association (AGA), and the American Society for Metabolic and Bariatric Surgery (ASMBS) reflect current advances in obesity science, antiobesity medication options and their rational clinical use and bariatric surgical and noninvasive options [4; 7; 30; 122; 123; 124; 125; 126].

THE FOUR PILLARS OF OBESITY MANAGEMENT

What are the four pillars of obesity care?

The OMA states that obesity is a serious and multifactorial disease that requires patient access to comprehensive care, including the four pillars of healthful nutrition, physical activity, behavior modification, and medical management with antiobesity medications and surgical interventions. Comprehensive care of obesity is not only about reducing weight but also about improving the health of patients [122].

Initial comprehensive care includes medical history, review of systems, personal history (e.g., family, socioeconomic, culture, nutrition, physical activity, behavioral, and eating disorder history), evaluation for primary and secondary causes of obesity, routine preventive care, physical exam, and laboratory testing [122]. Common metabolic complications of obesity include type 2 diabetes, hypertension, dyslipidemia, nonalcoholic fatty liver disease (NAFLD), and the fat mass complication of sleep apnea. "Treat obesity first" represents a standard of care for patients with obesity-related complications that can slow the progression of metabolic complications and reduce premature mortality [122].

Healthful Nutrition

The OMA recommends that patients with obesity have access to safe, effective, personalized, and evidence-based healthful nutritional intervention. Patients should optimally have access to nutrition therapy via a registered dietitian or via nutritional counseling from obesity medicine clinicians trained in nutritional counseling. Approaches to overcome barriers to nutritional intervention engagement include individual or group videoconferencing, personalized artificial intelligence (AI)-mediated interventions applicable to precision medicine, incorporation of cultural norms, and awareness of the impact of social determinants of health [122].

Physical Activity

The OMA recommends patients with obesity be treated with a safe and effective personalized physical activity plan (i.e., physical activity prescription) based on the patient's underlying health and mobility. To achieve physically active objectives, the OMA recommends that patients with obesity learn the benefits of non-exercise activity thermogenesis, target dynamic goals (e.g., steps per day), and safely incorporate resistance training. The intent is to improve body composition, support weight loss maintenance, improve balance and flexibility, and reduce the risk of injury from falls or joint stress. Improving or maintaining mobility can be achieved via training to promote activities of daily living (e.g., self-dressing, -meal preparation, -bathing, -laundry). Physical activity and exercise training may occur individually or in groups, via live classes/instruction, video format, or AI educational interactions, and may be especially important in patients with sarcopenic obesity [122].

Behavior Modification

The OMA recommends patients with obesity be treated with evidence-based behavior modification. Important aspects include personalized tracking and regular clinician encounters. Optimizing social support at home and in the community may be helpful. Patients often benefit from behavior modification provided by a knowledgeable physician, nurse practitioner, physician assistant, nurse, or dietitian, or via a psychologist/psychiatrist, health coach, or another appropriate counselor. For patients for which record keeping and accountability metrics may improve health outcomes, other potential interventions include fitness trackers, smartwatches, and use of social media. Behavior modification may also be delivered through AI chatbots [122].

The U.S. Preventive Services Task Force (USPSTF) recommends that clinicians offer or refer patients with a BMI of 30 or greater intensive, multicomponent behavioral interventions.

(https://jamanetwork.com/journals/jama/fullarticle/2702878. Last accessed November 28, 2023.)

Strength of Recommendation: B (The USPSTF strongly recommends that clinicians routinely screen eligible patients. The USPSTF found good evidence that obesity screening improves important health outcomes and concludes that benefits substantially outweigh harms.)

OBESOGENIC MEDICATIONS AND WEIGHT-NEUTRAL OR -REDUCING ALTERNATIVES			
Clinical Condition or Drug Class	**Weight-Promoting**	**Weight Neutral**	**Weight-Reducing**
Type 2 diabetes with obesity	Pioglitazone Sulfonylureas Insulin	DPP-4 inhibitors	Metformin SGLT2 inhibitors GLP-1R agonists
Antidepressants	Paroxetine Amitriptyline Mirtazapine	—	Bupropion Fluoxetine
Atypical antipsychotics	Olanzapine Quetiapine Risperidone	Ziprasidone	—
Anticonvulsants and mood stabilizers	Divalproex Carbamazepine Gabapentin	Lithium Lamotrigine	Zonisamide Topiramate
Inflammatory rheumatic diseases	Corticosteroids	DMARDs NSAIDs	—
DMARDs = disease-modifying antirheumatic drugs, DPP-4 = dipeptidyl peptidase-4, NSAIDs = nonsteroidal anti-inflammatory drugs, SGLT2 = sodium-glucose cotransporter-2.			
Source: [131]			*Table 6*

Medical Management

Antiobesity Medications

Medical treatment with antiobesity medication and/or bariatric procedures is the fourth pillar of obesity management. Evidence-based treatment of obesity, including pharmacotherapy, represents a standard of care for patients with obesity [122].

Obesity is associated with $174 billion in excess healthcare costs annually. To mitigate such expenditures, obesity should be treated early and effectively before its complications arise. In patients without acute complications of obesity, a "treat obesity first" approach through antiobesity medications may reduce or eliminate the need (and cost) for antidiabetic medications, antihypertension medications, lipid medications, pain medications, and possibly other medications (e.g., antidepressants) or other treatments (e.g., continuous positive airway pressure devices) [122].

When appropriate for the patient, use of lower-cost antiobesity medications may improve the cost effectiveness of medication. The forthcoming generic status of some current agents and market entry of new antiobesity medications may drive competition and lower costs [122]. However, the OMA stresses the importance of a patient-centered, personalized approach to pharmacotherapy for obesity and that such an approach may depart from the recommended prescribing information [122].

Bariatric Procedures

The OMA recommends that patients with obesity should have access to evidence-based bariatric procedures, when appropriate, as an adjunct to healthful nutrition, physical activity, behavior modification, and pharmacotherapy. Currently, less than 1% of eligible patients receive bariatric surgery, despite extensive evidence of its cost-effectiveness. Importantly, bariatric surgery is associated with reductions in overall mortality, cardiovascular events, risk of cancer, cardiovascular risk factors (e.g., type 2 diabetes, hypertension, dyslipidemia), and improvements in osteoarthritis, skin disorders, and possibly depression [116; 122; 127; 128; 129; 130].

OBESOGENIC MEDICATIONS

Obesity may result from an identifiable primary cause. Some endocrine disorders, including hypothalamic disorders, insulinoma, hypothyroidism, and hypercortisolism, are strongly associated with obesity or its onset [24]. A common culprit are drugs that promote weight gain, and a central task for clinicians caring for patients with obesity involves reviewing their use of obesogenic medications (***Table 6***) [131].

In chronic disease management, the weight-gain potential is often overlooked when choosing pharmacotherapy options. However, many commonly used medications associated with weight gain have alternatives with weight-neutral or weight-losing effects. Shifting medication choices from weight-positive to weight-neutral or -negative choices can be an effective means of facilitating weight loss [122].

Common medication classes associated with weight gain include steroids, antipsychotics, antiepileptics, glucocorticoids, and gabapentinoids. When these or other prescribed medication classes induce significant weight gain, especially to an extent that may exceed the positive treatment effects, switching patients to alternative medications that are weight-neutral or weight-loss-promoting should be considered within a shared decision-making process including the patient and prescribing provider (e.g., psychiatry, neurology, other specialists) [131].

For patients with type 2 diabetes and obesity requiring insulin therapy, adding metformin or GLP-1R agonists can reduce or nullify (with GLP-1R agonists) insulin-associated weight gain. Clinicians should add one of these agents when starting a patient with type 2 diabetes on insulin therapy. Among insulin therapies, basal insulin is associated with less weight gain than biphasic or prandial short-acting insulin and should be the first-line option [131].

Obesity and inflammatory rheumatic diseases commonly co-occur, with a hypothesized causal role due to the proinflammatory nature of adipose tissue. Patients with obesity have higher disease scores and poorer treatment response to disease-modifying antirheumatic drugs (DMARDs). Minimize or avoid corticosteroids, which tend to promote weight gain, in favor of nonsteroidal anti-inflammatory drugs (NSAIDs) and DMARDs [131].

PRIORITIZATION FOR PATIENTS WITH OBESITY AND CARDIOMETABOLIC DISEASE

Patients with acute metabolic abnormalities (e.g., marked hyperglycemia, uncontrolled hypertension, severe hypertriglyceridemia, cardiovascular disease, cancer) should have these illnesses urgently assessed and treated, preferably with concomitant interventions that may also improve obesity [128]. For most patients without acute illness, treatment of obesity is the priority, especially if the therapies chosen for treatment of the obesity are also expected to improve the complications of obesity [128]. In weight-loss pharmacotherapy, the initial priority should be to safely achieve maximal weight reduction, followed by sustained antiobesity medication and lifestyle therapy that may require less supervision to maintain the reduced body weight [132].

TREATING TO TARGET WITH ANTIOBESITY MEDICATIONS

Obesity is a chronic disease that involves more than excessive body fat. The fat mass leads to biomechanical complications, such as obstructive sleep apnea and osteoarthritis. The pathogenic adipose tissue promotes cardiometabolic disease, which begins with subclinical insulin resistance that eventually produces metabolic syndrome, prediabetes, hypertension, dyslipidemia, and hepatic steatosis. These conditions indicate risk for progression to the end-stage manifestations of cardiometabolic disease, namely type 2 diabetes, NASH, and cardiovascular disease. The development of obesity exacerbates insulin resistance and impels progression of cardiometabolic disease toward these ultimate outcomes. As with other chronic diseases, the complications of obesity impair health and confer morbidity and mortality [3].

In treating obesity as a chronic disease, the essential goal of weight-loss therapy is not the quantity of weight loss per se, but rather the prevention and treatment of complications to enhance health and mitigate morbidity and mortality. This paradigm of care is the basis of the complications-centric AACE/ACE obesity guideline and the diagnostic term adiposity-based chronic disease (ABCD) [3].

The degree of efficacy and safety with second-generation antiobesity medications (e.g., semaglutide) and better understanding of obesity as a chronic disease has made possible a treating-to-target paradigm using percent total weight loss as a biomarker that can actively be managed within a range associated with optimal outcomes [123].

A treat-to-target approach has abundant precedent in medicine. In diabetes, clinicians treat the biomarker HbA1c to a target of ≤7.0% or ≤6.5%, because this will minimize micro- and macrovascular complications. Hypertension involves control of blood pressure levels to prevent cardiovascular and renal complications. To prevent and treat cardiovascular disease, LDL-C serves as a biomarker that is managed to a level based on patient risk estimates. In each instance, treatment to target for each biomarker (HbA1c, blood pressure, and LDL-C) is individualized based on an individual patient's overall risk, other comorbid conditions, and natural history of the disease [3].

Similarly, percent total weight loss is a more appropriate biomarker than body weight or BMI. Second-generation antiobesity medications allow clinicians to reach targets of weight loss that will predictably treat or prevent a broad spectrum of complications in ABCD [3]. Weight reductions of ≥10%, ≥15%, or 20% or more may be required for improvement in certain weight-related complications and are often more desired therapeutic goals in clinical practice [133]. Depending on the complication profile, the target for percent total weight loss can be individualized [3].

The estimated weight reduction required to improve morbidity and mortality outcomes are [3]:

- 5% to 10% weight reduction: Improved physical and biomechanical function, type 2 diabetes prevention
- 10% to 15% weight reduction: Cardiovascular disease risk reduction and remission/reduction in obstructive sleep apnea, hypertension, type 2 diabetes hyperglycemia
- ≥16% weight reduction: Type 2 diabetes remission, NASH improvement

These figures are mostly relevant to noninvasive obesity interventions. The long-term reduction and remission of metabolic disorders attainable with bariatric surgery has led to their renaming as metabolic and bariatric surgery [126].

ANTIOBESITY MEDICATIONS

Lifestyle modification is considered the primary treatment of obesity. A meta-analysis of 31 randomized controlled trials assessing lifestyle versus control interventions showed an average 3.6-kg weight loss at one year and 2.5-kg at three years [134]. Unfortunately, most people cannot achieve sufficient weight loss or maintain it long-term without pharmacotherapy or surgery [135].

However, effective pharmacological interventions for obesity have historically been challenging to achieve. The reasons are complex and include both behavioral and biological factors, which are difficult to separate from each other. Physiologically, metabolic adaptations in response to energy deficits and weight reduction defend against sustained fat mass loss. In the CNS, redundant pathways favor a state of anabolic and orexigenic activity. Thus, efforts to develop pharmaceutical agents that can overcome these strong neurobiological defenses, while limiting adverse effects, has proven to be somewhat elusive [123].

In 1937, during clinical trials evaluating amphetamine (Benzedrine) for the treatment of depression and narcolepsy, it was noted that subjects lost weight. Amphetamines became widely used weight-loss drugs during the 1940s and 1950s but were associated with numerous side effects [136]. After World War II, researchers discovered that injecting norepinephrine into the CNS of experimental animals reduced food intake and activated thermogenesis, prompting a search for thermogenic drugs that could work through monoaminergic receptors [4]. This resulted in sympathomimetic amines, which modified the molecular structure of amphetamine to mitigate the undesirable side effects, with phentermine, diethylpropion, phendimetrazine, and benzphetamine approved for short-term weight loss and remain available for this indication [3].

The duration required of antiobesity pharmacotherapy was thought to be around 12 weeks, the length of time needed to break a bad habit or learn to ride a bicycle without training wheels [136]. Due to a limited understanding of obesity pathophysiology, it was believed that once weight was lost, ongoing treatment was unnecessary [3]. Obesity was recognized as a disease by the scientific community in 1985, but it was not until 2013 that obesity was acknowledged as a chronic disease by the American Medical Association [136].

Orlistat, which impairs intestinal fat absorption, was approved in 1999 for chronic weight management, but medications were needed for long-term use that could blunt appetite by counteracting abnormalities in the gut-brain axis. Three such medications were approved by the FDA—fenfluramine, sibutramine, and lorcaserin—were prominently serotonergic drugs, but all have been discontinued due to safety concerns [3].

Rimonabant, the first CB-1 receptor antagonist, was approved in Europe, but not by the FDA because of concerns about suicidality. Due to psychiatric side effects, marketing of rimonabant was suspended in Europe in 2008, two years after its approval as an antiobesity medication.

From 2012 to 2014, three centrally acting antiobesity medications were approved for chronic weight management that remain available: phentermine/topiramate extended-release (ER), naltrexone/bupropion ER, and liraglutide. Semaglutide was approved in 2021 [3].

Similar to several other antiobesity medications, GLP-1 receptor agonists (GLP-1 RAs) became used in obesity following observations of weight loss in other clinical populations. Liraglutide, semaglutide, and tirzepatide were approved for the treatment of type 2 diabetes before their efficacy as antiobesity medications was evaluated.

The introduction of semaglutide marks a watershed in the history of nonsurgical obesity treatment. Semaglutide essentially doubled the weight loss observed with existing obesity medications, ushering in the era of second-generation antiobesity medications [3]. Tirzepatide surpasses the weight-loss efficacy of semaglutide.

INDICATIONS FOR USE

Except for setmelanotide and metreleptin, all antiobesity medications are approved as adjuncts to a reduced-calorie diet and increased physical activity for chronic weight management in adults with obesity (BMI ≥30) or overweight (BMI ≥27) with at least one weight-related complication, such as hypertension, type 2 diabetes, or dyslipidemia [137]. All antiobesity medications are considered pregnancy risk factor category X drugs and should not be prescribed to a patient who is pregnant, breastfeeding, or trying to conceive [124].

Randomized controlled trials of antiobesity medications mirror the FDA's indications in their inclusion criteria (BMI ≥30 or ≥27 with weight-related complication) and use as adjunct to lifestyle intervention. Whether participants are randomized to placebo or active drug, all receive a standardized lifestyle intervention: healthy meals, a deficit of 500 calories daily, 150 minutes of physical activity weekly, and regular dietitian counseling to help with meals and adherence [133; 138]. Infrequent variations are possible and are discussed later in this section.

The FDA indications may not adequately reflect current evidence. In 2018, the Endocrine Society endorsed pharmacotherapy as a first-line treatment for weight loss in patients with severe weight-related complications and removed the criteria of failed lifestyle modification [4]. A Korean obesity guideline endorses pharmacotherapy for patients with BMI ≥25, or ≥23 with weight-related complications, which may be applied to Asian populations in the United States [135; 139].

Many antiobesity medications were initially evaluated for efficacy in clinical trials of type 2 diabetes. Weight loss is considerably lower in patients with obesity and type 2 diabetes than in those without diabetes. Insulin resistance and chronic hyperglycemia correlate with diminished efficacy of GLP-1 RAs, which also argues for earlier intervention before metabolic organs are irreversibility damaged [132].

Obesity should be considered a chronic condition requiring long-term treatment, as most patients who stop pharmacotherapy are prone to weight gain. If lifestyle modification and drug therapy fail, bariatric surgery should be considered a sustainable weight loss option [135].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Department of Veterans Affairs and the Department of Defense suggest offering prescribed pharmacotherapy (specifically liraglutide, naltrexone/bupropion, orlistat, or phentermine/topiramate) for long-term weight loss in patients with a BMI ≥30 kg/m^2 and for those with a body mass index ≥27 kg/m2 who also have obesity-associated conditions, in conjunction with a comprehensive lifestyle intervention.

(https://www.healthquality.va.gov/guidelines/CD/obesity/VADoDObesityCPGFinal5087242020.pdf. Last accessed November 28, 2023.)

Strength of Recommendation: Weak for

FDA-APPROVED AGENTS

For Monogenic Obesity Syndromes

Setmelanotide (Imcivree)

For whom is setmelanotide contraindicated?

Setmelanotide is the first antiobesity medication approved specifically for the treatment of rare genetic conditions associated with obesity. The drug binds to melanocortin-4 receptor (MC4R) in the hypothalamus, downstream of the leptin signaling pathway [135]. Setmelanotide re-establishes the activity of the MC4R pathway, thus reducing hunger and promoting body weight loss by lowering caloric intake and increasing energy expenditure [140].

Setmelanotide is indicated for patients with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin-leptin receptor (LEPR) deficiency. The condition must be confirmed by genetic testing demonstrating pathogenic variants in *POMC*, *PCSK1*, or *LEPR* genes [30]. Setmelanotide is contraindicated for patients with other causes of obesity, polygenic obesity, or benign variants of the gene mutations. Dosing is subcutaneous 2 mg daily (maximum: 3 mg daily). Adverse effects include hyperpigmentation, vomiting, and nausea [135]. Setmelanotide is not associated with adverse effects on blood pressure observed with other MC4R agonists [141].

Bremelanotide

Bremelanotide is another MC4R agonist that also binds to MC3R and is FDA-approved for treatment of low sexual desire in premenopausal women. Data from two small randomized controlled trials in premenopausal women with obesity showed reduced caloric intake and weight loss with bremelanotide, without adverse effects on blood pressure, suggesting this may be an effective treatment of obesity [141].

Metreleptin

Metreleptin is a synthetic leptin analog approved by the FDA in 2014 for patients with congenital leptin deficiency or congenital/acquired lipodystrophy and is administered subcutaneously once daily. The recommended starting daily dose in adults with body weight ≤40 kg is 0.06 mg/kg (maximum: 0.13 mg/kg daily), while adults with body weight >40 kg are started on 2.5 mg or 5 mg for men or women, respectively (maximum: 10 mg daily). No leptin analog has been approved by the FDA or European Medicines Agency (EMA) as an antiobesity medication for generalized obesity [92].

For Short-Term Use: Sympathomimetic Amines

Phentermine, diethylpropion, phendimetrazine, and benzphetamine were approved for short-term use as antiobesity medications in 1959–1960, before obesity was understood as a chronic disease requiring long-term management. As a consequence, long-term (one year or longer) data on these drugs are limited [3].

All sympathomimetic amines are contraindicated in patients with hyperthyroidism, glaucoma, or in patients taking monoamine oxidase (MAO) inhibitors; all four are DEA Schedule IV controlled substances [131].

Phentermine (Adipex-P, Lomaira)

Phentermine HCl is a centrally acting sympathomimetic, with therapeutic effects mediated through increased levels of norepinephrine in the hypothalamus [123]. It was approved for short-term use in 1959 based on a 36-week trial that showed a mean placebo-subtracted weight loss of 8.2 kg [92]. Two more recent randomized controlled trials in Korea confirmed the short-term efficacy of phentermine, both showing significant weight reduction compared with placebo over 12 weeks [131].

Common adverse effects in clinical trials include dry mouth (55%) and insomnia (34%), without significant differences in systolic or diastolic blood pressure, headache, or palpitations between phentermine and placebo groups [131]. Other common side effects include dizziness, flushing, fatigue, and constipation [92]. Phentermine is not recommended for patients with cardiovascular disease, and uncontrolled hypertension is a relative contraindication. Phentermine is available in 8-mg tablets taken three times daily and in 15-mg, 30-mg, and 37.5-mg capsules taken once daily [131].

Phentermine is the most commonly prescribed antiobesity medication and is discussed further in the section on clinical use of antiobesity medications as a potential low-cost generic option to more recently approved agents.

Diethylpropion (Tenuate)

Diethylpropion and bupropion are very closely related structurally [142]. In contrast to phentermine, diethylpropion has been used infrequently in the United States. This contrasts with Mexico, Brazil, and other countries in which diethylpropion is a preferred antiobesity medication and where recent randomized controlled trials have evaluated its safety and efficacy. Outside the United States, diethylpropion is called amfepramone [143].

In one study, weight loss after 52 weeks was greater in patients randomized to diethylpropion than placebo (10.0 kg vs 3.1 kg), and more participants achieved weight loss ≥5% (71.4% vs 33.3%) [144]. Of 156 patients randomized to diethylpropion (75 mg/daily) or placebo, mean weight loss at three months (4.9 kg vs 0.7 kg) and six months (7.7 kg vs 1.1 kg) showed clinical benefit persisting beyond the short-term. Improvements in triglycerides, heart rate, and systolic and diastolic blood pressure with diethylpropion were non-significant [145].

Potential adverse effects of diethylpropion are dry mouth and somnolence (most common), constipation, anxiety, and irritability, all described as mild and nonpersistent, except dry mouth [143; 144; 145].

Diethylpropion is available in 25-mg short-acting and 75-mg extended-release tablets that are taken three times or once per day, respectively [136].

Other Medications

In analyses of two small 12-week randomized controlled trials, phendimetrazine (Obezine) appears to have similar weight-loss effects as other noradrenergic drugs [146].

Benzphetamine (Didrex) is the least prescribed among the four noradrenergic antiobesity medications, and there are few data from controlled trials evaluating its safety or efficacy [136].

For Long-Term Use

Gelesis100 Oral Hydrogel (Plenity)

Gelesis100 superabsorbent hydrogel is ingested orally, similar to drugs, but is regulated by the FDA as a class II medical device, because it acts mechanically as a transient, space-occupying device in a swallowed capsule that absorbs water to expand and fill up the stomach to induce satiety. Gelesis100 is FDA approved for patients with BMI 25–40. Recommended dosing is three capsules (2.25 g/dose) with water before both lunch and dinner [30; 123].

After 24 weeks, more patients on Gelesis100 than placebo had weight loss >5% (58.3% vs 42.3%) and >10% (27.4% vs 15.0%), but the mean weight loss difference (2.02%) did not meet the pre-determined threshold of 3%. The AGA guideline recommends the use of Gelesis100 be limited to clinical trials due to its uncertain benefit [123].

Orlistat (Xenical, Alli)

Why does the AGA obesity guideline suggest against the use of orlistat?

Orlistat is a pancreatic and gastric lipase inhibitor that blocks the lipase-catalysed breakdown and absorption of around 30% of dietary fats. Orlistat is the only antiobesity medication that does not exert action in the brain; its modest weight-loss effect depends mostly on diet [147].

Orlistat is available in 60-mg capsules over the counter and 120-mg capsules by prescription, both taken three times daily [131]. In the four-year XENDOS trial that randomized 3,304 subjects with obesity to orlistat (120 mg three times daily) or placebo, weight loss was significantly higher with orlistat (5.8 kg vs 3.0 kg). The study also showed a reduced progression from prediabetes to diabetes with orlistat. Adverse effects observed in ≥10% of study populations included rectal leakage, abdominal pain, abdominal stress, flatulence with discharge, fecal urgency, steatorrhea, fecal incontinence, and increased defecation [140].

Overall weight loss with orlistat is of a small magnitude (2.78%). In contrast, the adverse effects are considered very bothersome and result in high treatment discontinuation rates. Therefore, the 2022 AGA obesity guideline suggests against the use of orlistat [123].

Phentermine/Topiramate ER (Qsymia)

Topiramate is an antiepileptic drug that was approved for seizures in 1996 and migraine prevention in 2004. The weight loss observed during epilepsy treatment led to clinical trials as a treatment for obesity, but topiramate development as an antiobesity medication was discontinued due to the associated adverse effects. However, clinical observations in private practice indicated that phentermine mitigated topiramate adverse effects and increased weight-loss efficacy when used together. This led to clinical trials to approve the combination as an antiobesity medication [136].

Topiramate is thought to suppress appetite by increasing dopamine release, inhibiting glutamate receptors, and modulating neuropeptide-Y, an orexigenic hormone. Phentermine/topiramate was approved in 2012 at fixed-dose 7.5/46-mg and 15/92-mg tablets, both taken once-daily [131].

Three phase 3 randomized controlled trials assessed the efficacy of phentermine/topiramate on weight loss: EQUIP, CONQUER and SEQUEL. In EQUIP, patients with obesity (mean BMI: 42) were randomized to 3.75/23 mg, 15/92 mg, or placebo. Mean weight loss was 5.1% (low-dose), 10.9% (high-dose), and 1.5% (placebo) at 56 weeks [140].

CONQUER randomized 2,487 adults with overweight or obesity and at least two weight-related complications to placebo, 7.5/46 mg, or 15/92 mg. Mean weight loss (1.4 kg, 8.1 kg, and 10.2 kg, respectively) and patients with ≥5% (21%, 62%, and 70%, respectively) and ≥10% (7%, 37%, and 48%, respectively) weight loss at 56 weeks were significantly greater with both phentermine/topiramate dose levels [131].

SEQUEL was a 52-week extension of CONQUER involving 676 subjects [148]. At week 108, mean weight loss from baseline was 1.8%, 9.3%, and 10.5% with placebo, 7.5/46 mg, and 15/92 mg, respectively. Absolute weight loss was 2.1 kg, 9.6 kg, and 10.9 kg. Across all levels, weight loss was greater for subjects in the treatment arms than in the placebo group, with more kilograms lost among the higher dosage. After 108 weeks, 50.3% and 53.9% of patients receiving phentermine/topiramate lost at least 10% of their body weight; 9.2% and 15.3% lost 20% or greater. This compares with 11.5% and 2.2%, respectively, of participants in the placebo group. At week 108, mean waist circumference reductions were -3.6 cm for placebo, -9.8 cm for the 7.5/46-mg dose, and -10.6 cm for the 15/92-mg group. The types of adverse events in SEQUEL were similar to those in CONQUER, but the incidence was markedly lower in the second year. Drop-out due to adverse events by week 108 were 3.1%, 4.5%, and 4.4% in placebo, 7.5/46 and 15/92 treatment arms. Both systolic and diastolic blood pressure decreased from baseline by 3–5 mm Hg at 108 weeks in all three treatment arms [148].

As with phentermine monotherapy, phentermine/topiramate ER is not recommended for patients with cardiovascular disease and is contraindicated in patients with hyperthyroidism or glaucoma or in those taking MAO inhibitors [131]. Topiramate is associated with cognitive and neuropsychiatric side effects. A meta-analysis found that, compared with placebo, adverse effects associated with phentermine/topiramate included dysgeusia or altered sense of taste, paresthesia, dry mouth, disturbance in attention, irritability, hypoesthesia, constipation, and dizziness [149]. Abrupt withdrawal of topiramate increases the risk of seizures, and downward titration should be gradual over four to five days [150].

During the two-year SEQUEL trial, the incidence of reported anxiety-related adverse events increased with dose in placebo (3.1%), 7.5/46-mg (6.5%), and 15/92-mg (9.5%) arms. Most were mild in severity, but three subjects in the 15/92-mg group experienced a severe anxiety-related adverse events and one discontinued treatment [148].

Topiramate is teratogenic, posing a risk for orofacial clefts in infants exposed in utero. Women of childbearing age prescribed any topiramate formulation should be counseled to use effective contraception [124].

Naltrexone/Bupropion ER (Contrave)

Bupropion is a norepinephrine and dopamine reuptake inhibitor with FDA-approval for depression and smoking cessation and is the antidepressant least likely to induce weight gain [131]. Bupropion stimulates hypothalamic POMC neurons, releasing α-MSH (which bind MC4R), decreasing food intake, and increasing energy expenditure. When α-MSH is released, POMC neurons also release β-endorphin, a μ-opioid receptor (MOR) ligand, which inhibits further release of α-MSH by activating a negative feedback loop. Naltrexone, an opioid receptor antagonist approved for the treatment of alcohol and opioid use disorder, blocks the β-endorphin-mediated negative feedback; the subsequent increase in POMC activity may underlie the weight loss effects of naltrexone/bupropion (Contrave) [115].

Each naltrexone/bupropion tablet contains naltrexone 8 mg plus bupropion 90 mg. The target maintenance dose of 4 tablets daily (naltrexone 32 mg/bupropion 360 mg) daily is shortened with the prolonged-release formulation (NB32). The initial dose is 1 tablet daily, increased stepwise to the target of 2 tablets twice daily. Typical weight loss seen in practice is around 5% to 6% with NB32s [131].

The Contrave Obesity Trials (COR) program evaluated NB32 versus placebo over 56 weeks in patients with obesity or overweight and weight-related complication(s) (COR-I, COR-II, and COR-BMOD) and in patients with obesity and type 2 diabetes (COR-DM). Mean weight loss with NB32 compared with placebo in COR-I (6.1% vs 1.3%), COR-II (6.4% vs 1.2%), COR-BMOD (9.3% vs 5.1%), and COR-DM (5.0% vs 1.8%) showed an average 4.35% weight loss advantage over placebo [139].

Common adverse effects of NB32 include nausea (30%), headache (14%), and constipation (15%), without significant differences in depression or suicidality events, insomnia, dizziness, or dry mouth between treatment and placebo groups [131]. NB32 has been shown effective in reducing HbA1c and is safe among subjects with type 2 diabetes taking oral antidiabetic agents [151]. NB32 can increase blood pressure and pulse despite weight loss [139]. While the cardiovascular safety of NB32 was investigated in the LIGHT trial, it was terminated prematurely after the study sponsor publicly released confi-

dential favorable interim results after only 25% of expected vascular events had accrued, making it difficult to interpret the cardiovascular safety of this combination drug [131; 139].

Contraindications include pregnancy, uncontrolled hypertension, seizure disorder, eating disorder, severe hepatic dysfunction, and concurrent administration of MAO inhibitors [131]. Naltrexone/bupropion is contraindicated in any patient prescribed opioids for pain control and in any patient receiving medication therapy for alcohol or opioid use disorder.

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs)

Endogenous GLP-1 has a very short half-life due to rapid enzymatic degradation by dipeptidyl peptidase-4 (DPP-4). Synthetic analogs modify the GLP-1 structure to resist DPP-4 by amino acid substitutions in the protein structure or by attachment to large proteins such as albumin or immunoglobulin [147]. Liraglutide shares a 97% amino acid sequence similarity with human GLP-1, while semaglutide has a 94% similarity. Compared with liraglutide, the substantially longer half-life and greater weight loss efficacy of semaglutide may involve differences in the attached fatty acids [139].

Liraglutide and semaglutide are used subcutaneously once-daily and once-weekly, respectively. Liraglutide was approved for type 2 diabetes in 2010 at a dosage of 1.8 mg daily. Subsequently, liraglutide became the first GLP-1 RA approved as antiobesity medication in 2014, and in 2020, its approval was expanded to include adolescents (12 years of age or older) at a dosage of 3.0 mg/day [147]. Liraglutide acts centrally on the arcuate nucleus in the hypothalamus to suppress appetite and potentiate satiety [151].

The SCALE Obesity and Prediabetes and SCALE Diabetes were both 56-week randomized controlled trials examining the effect of daily liraglutide 3.0 mg vs placebo on normoglycemia, prediabetes, and diabetes. Both trials demonstrated significantly greater weight loss with liraglutide. In SCALE Obesity and Prediabetes, weight loss was 8.0% with liraglutide vs 2.6% with placebo; in SCALE Diabetes, weight loss was 6.0% with liraglutide vs 2.0% with placebo. In the former trial, more participants in the liraglutide group achieved weight loss of ≥5% (63.2 vs 27.1%), ≥10% (33.1 vs 10.6%), and ≥15% (14.4 vs 3.5%) [131].

Gastrointestinal adverse effects are common, including nausea (40%), diarrhea (20%), constipation (20%), and vomiting (16%), and were the most common reason for liraglutide drop-out (6.4% vs 0.7% in the placebo group). Potentially serious adverse effects include gallbladder disease (2.5%) and pancreatitis (0.4%) [131]. A 2023 analysis of data including more than 5,000 patients receiving pharmacotherapy for obesity compared the incidence of adverse events associated with GLP-1 RAs with bupropion-naltrexone. Use of GLP-1 agonists compared with bupropion-naltrexone was associated with increased risk of pancreatitis (hazard ratio: 9.09), bowel obstruction (hazard ratio: 4.22), and gastroparesis (hazard ratio: 3.67) but not biliary disease [152].

Liraglutide is initiated at 0.6 mg daily for one week, with weekly increases in dose (by increments of 0.6 mg) to the recommended 3.0 mg dose [131]. Semaglutide was initially approved for the treatment of type 2 diabetes at a dosage of 1.0 mg weekly in 2017 and at 2.0 mg weekly in 2022. It was subsequently approved at a dosage of 2.4 mg per week for chronic management of obesity in 2021 [147].

Semaglutide directly accesses the hypothalamus, brainstem, and septal nucleus and also induces activation in secondary brain areas without direct GLP-1R interaction, thus having direct and indirect effects on neutral pathways involved in homeostatic (appetite, hunger, satiety) and hedonic (food preference, cravings, control of eating) aspects of food intake and reward-related eating behaviors. Conversely, only a very small percentage of weight loss is explained by delayed gastric emptying and gastrointestinal side effects [151].

The STEP clinical trials program evaluated semaglutide 2.4 mg in patients with obesity or overweight/weight-related complication(s); patients with type 2 diabetes were excluded [30]. At 68 weeks, semaglutide led to greater mean weight loss (14.9%) compared with placebo (2.4%); further, more patients in the semaglutide group experienced weight loss of ≥10% (69.1%), ≥15% (50.5%), and ≥20% (32.0%) than those in the placebo group (12.0%, 4.9%, and 1.7%, respectively).

In an extension of this study, patients in both the treatment and control arms were engaged in intensive behavioral therapy. The therapy consisted of a reduced-calorie diet (1,000–1,200 calories/day for the first seven weeks, followed by 1,200–1,800 calories/day for the remaining study period), 200 minutes exercise per week, and 30 individual therapy sessions with a registered dietitian. The mean weight loss was 16.0% with semaglutide/intense behavioral therapy, compared with 5.7% with placebo and intense behavioral therapy. The authors concluded that intense behavioral therapy plus eight-week low-calorie diet ultimately may not confer significant weight-loss advantages beyond those achieved with semaglutide and less-intensive lifestyle interventions (i.e., 18 behavioral counseling sessions over 68 weeks) [30].

Another extension of the study, referred to as STEP 4, focused on weight-loss maintenance. All patients were initiated on semaglutide and, at week 20, were randomized to either semaglutide continuation or placebo for the remaining 48 weeks (i.e., weeks 20–68). The semaglutide continuation group further lost 8% of weight, for a total 17% weight loss. The placebo group gained 7% of weight during the same period, for a total 5% weight loss.

STEP 5 also examined the durability of weight reduction over two years. At week 104, mean weight loss from baseline was 15.2% with semaglutide compared with 2.6% with placebo (treatment difference: 12.6%).

Finally, STEP 8 was a head-to-head comparison of semaglutide 2.4 mg per week and liraglutide 3.0 mg per day over 68 weeks. Mean weight loss was 6.4% with liraglutide and 15.8% with semaglutide, a 9.4% advantage over liraglutide. While gastrointestinal adverse events were similarly common with semaglutide (84.1%) and liraglutide (82.7%), the drop-out rate due to adverse events was significantly higher with liraglutide than semaglutide (12.6% vs 3.5%) [140].

As of 2023, oral semaglutide is the only oral GLP-1 RA approved for the treatment of type 2 diabetes, at a dosage of 14 mg per day (Rybelsus). Higher doses are being investigated for weight effects in obesity without type 2 diabetes in the OASIS trials [147]. The phase 3 OASIS 1 trial assessed oral, once-daily semaglutide 50 mg in 667 adults with obesity without type 2 diabetes. After 68 weeks, participants on semaglutide had greater mean weight loss (15.1% vs 2.4%), weight loss ≥10% (69% vs 12%), ≥15% (54% vs 6%), and ≥20% (34% vs 3%) compared with placebo. Adverse effects (mostly mild-to-moderate gastrointestinal symptoms) occurred in 80% on semaglutide and 46% on placebo. These outcomes mirror those of semaglutide 2.4 mg subcutaneous [153]. Phase 3 trials have completed, and submission for FDA approval is expected in 2024. Of note, there are currently no registered clinical trials comparing oral with subcutaneous semaglutide for obesity [92].

The liraglutide, semaglutide, and tirzepatide labels carry a boxed warning regarding the risk of thyroid C-cell tumors. All three antiobesity medications are known to cause dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in rodents [20; 137]. It is unknown whether semaglutide for obesity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined. However, semaglutide for obesity is contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2) [20; 137]. All patients should be counseled regarding the potential risk of MTC and symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

In addition, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists [20; 137]. These agents have not been studied in patients with a history of pancreatitis; if used as an antidiabetic agent, clinicians should consider an alternate option in such patients.

Data are lacking on use in pregnant women. However, reproduction studies in animals have shown teratogenic effects. There is no published research linking semaglutide to decreased oral contraceptive efficacy. However, any medication associated with delayed gastric emptying could theoretically impact the absorption of oral contraceptive agents.

A meta-analysis of treatment with GLP-1 RAs found liraglutide or dulaglutide associated with increased risk for gallbladder or biliary diseases; subcutaneous semaglutide and exenatide associated with non-significant increased risk; and higher-dose subcutaneous semaglutide associated with increased gallbladder or biliary diseases. Oral semaglutide, lixisenatide, and albiglutide are not associated with these increased risks [154].

GLP-1 RAs may be associated with increased risk of gallbladder or biliary diseases because GLP-1 inhibits gallbladder motility and delays gallbladder emptying by suppressing cholecystokinin secretion. The risk of gallbladder or biliary diseases was higher in trials for weight loss than diabetes control, which may relate to the greater weight loss, GLP-1 RA dose, or treatment duration [154]. When assessing potential risk to patients, prescribers should consider the denominator for essential context, when possible. The overall absolute risk increase, an additional 27 cases per 10,000 persons treated per year, was small and should be weighed against the demonstrated benefits of obesity treatment with GLP-1 RAs [154].

Tirzepatide

Tirzepatide was approved for type 2 diabetes treatment by the FDA (as Mounjaro) and the European Medicines Agency in 2022 [147]. In 2023, the FDA approved the agent for chronic weight management [155].

Tirzepatide acts as a dual incretin agonist of GLP-1R and glucose-dependent insulinotropic polypeptide (GIP) receptor and is dubbed the "twincretin" [135]. Tirzepatide has five-fold greater potency at GIPR than GLP-1R [132].

GIP was the first incretin hormone identified, but its therapeutic potential was disregarded because chronic hyperglycemia in type 2 diabetes down-regulates GIPR expression in β-cells, blunting response to GIP. Normalizing blood glucose can restore GIPR sensitivity to GIP [139; 147]. With a GIP/GLP-1 receptor agonist, GLP-1 quells the potential glucagon-stimulatory effects of GIP and (re)sensitizes β-cells to GIP's incretin effects, while potentially enhancing GIP's beneficial effects on weight regulation mechanisms [147].

GIPR agonism may have effects on adipocytes that include increasing lipoprotein lipase, promoting lipogenesis, enhancing fatty acid and glucose uptake, and inhibiting lipolysis mediated by glucagon and adrenergic receptors [139]. However, the relative contributions of GLP-1R vs GIPR agonist effects to weight loss have yet to be clearly defined [156].

SURMOUNT-1 WEIGHT-LOSS OUTCOMES AT 72 WEEKS				
Weight Loss Parameter	**Tirzepatide**			**Placebo**
	5 mg	**10 mg**	**15 mg**	
Mean weight loss	15.0%	19.5%	20.9%	3.1%
≥5% weight loss	85.1%	88.9%	90.9%	34.5%
≥10% weight loss	68.5%	78.1%	83.5%	18.8%
≥15% weight loss	48.0%	66.6%	70.6%	8.8%
≥20% weight loss	30.0%	50.1%	56.7%	3.1%
≥25% weight loss	15.3%	32.3%	36.2%	1.5%
Mean reduction in waist circumference	14.0 cm	17.7 cm	18.5 cm	4.0 cm

Source: [133] *Table 7*

SURPASS-1 compared tirzepatide (5 mg, 10 mg, or 15 mg) to placebo for 40 weeks, finding significant mean reductions in hemoglobin A1C (-1.87%, -1.89%, -2.07%) and body weight (-7.9%, -9.3%, -11.0%) for all tirzepatide doses versus placebo [131]. SURPASS-2 compared tirzepatide (5 mg, 10 mg, or 15 mg) with semaglutide 1.0 mg weekly, finding more effective and dose-dependent reductions in body weight, blood pressure, and hemoglobin A1C with tirzepatide [131]. (Note that semaglutide 1.0 mg is a subtherapeutic dose for weight-loss efficacy.)

SURMOUNT-2 randomized 1,514 adults to tirzepatide or placebo. At week 72, mean weight loss with tirzepatide 10 mg or 15 mg or placebo was 12.8%, 14.7%, and 3.2%, respectively. This translated to mean differences vs placebo of 9.6% and 11.6% for 10 mg and 15 mg. More participants had weight loss ≥5% with tirzepatide (79% to 83%) than placebo (32%). The most frequent adverse effects with tirzepatide were gastrointestinal-related, including nausea, diarrhea, and vomiting, mostly mild to moderate in severity, and few led to drop-out (<5%). Serious adverse events were reported by 7% of participants overall [157].

In the phase 3 SURMOUNT-1 trial, 2,539 patients with obesity without type 2 diabetes were randomized to weekly tirzepatide (5 mg, 10 mg, or 15 mg) or placebo [133]. Mean weight loss at week 72 was unprecedented (***Table 7***) [131]. Notably, 50% and 57% of participants in the 10- and 15-mg groups had weight loss ≥20% [131]. For the first time ever, weight loss with a medication approached levels that had only been possible with bariatric surgery.

Drop-out from adverse effects was 4.3%, 7.1%, and 6.2% with 5 mg, 10 mg, and 15 mg tirzepatide, respectively, and 2.6% with placebo. The incidence of adverse effects was similar in 10- and 15-mg groups, while the proportion of ≥10%, ≥15%, and ≥20% weight-loss was higher with 15 mg. This suggests the 15-mg dose may confer additional benefits in some patients without added safety concerns [133].

Participants treated with tirzepatide had a percent reduction in fat mass approximately three times greater than the reduction in lean mass, resulting in an overall improvement in body composition. The ratio of fat-mass loss to lean-mass loss is similar to lifestyle and surgical treatments for obesity [133].

Nearly all participants (>95%) with prediabetes initiated on tirzepatide converted to normoglycemia by 72 weeks (compared with 62% with placebo plus lifestyle changes). These improvements may translate to reduced risk of cardiovascular disease, chronic kidney disease, NAFLD, and type 2 diabetes, among other outcomes. Studies of this are still in progress [133].

The safety profile of tirzepatide was consistent with previous findings in the SURPASS trials in patients with type 2 diabetes and similar to other incretin-based therapies for the treatment of obesity. Cholecystitis was observed more frequently with tirzepatide, but the low incidence (≤0.6%) made causal conclusions difficult. Gallbladder-related events have been reported to increase in persons with considerable weight reduction and are also observed with other obesity therapies, such as bariatric surgery and treatment with GLP-1 receptor agonists [133].

Meta-analyses have variously examined the effectiveness and safety of tirzepatide compared with semaglutide in obesity. Head-to-head comparative trials have not been conducted, so indirect comparisons were used. One analysis found greater weight loss with tirzepatide 10 mg and 15 mg than semaglutide 2.4 mg [158]. Another found no significant difference from semaglutide in gastrointestinal adverse effects [159]. Together, these trials show promise for tirzepatide as an effective and safe medication for both weight reduction and glycemic control in patients with obesity with or without type 2 diabetes. Typical adverse effects are similar to GLP-1 agonists and include nausea, vomiting, and diarrhea. No clinically significant hypoglycemia was reported in any trial [131].

GLP-1 RAs provide substantial benefits in glycemic control and weight loss while improving health-related quality of life among individuals with type 2 diabetes. GLP-1 RAs have also been shown to significantly decrease the risk of cardiovascular and all-cause mortality in type 2 diabetes, producing a significant reduction in the risk for non-fatal myocardial infarction and non-fatal stroke. However, their impact on heart failure-related outcomes is nil [160].

Compared with semaglutide in subjects with type 2 diabetes, tirzepatide produced significantly more improvements in total insulin secretion and insulin sensitivity, reflecting a significant improvement in pancreatic β-cell function. Similar effects were also documented in another trial comparing tirzepatide with the GLP-1 RA dulaglutide, suggesting that dual receptor agonism might be responsible for improving insulin sensitivity, especially since the observed effect was only partially attributable to weight loss [160].

The question that inevitably arises is whether tirzepatide is more efficacious and equally safe compared with GLP-1 RAs. When tirzepatide was compared with GLP-1 RAs, it was not associated with a significant increase in the odds of nausea, vomiting, or diarrhea, except for tirzepatide 10 mg, which correlated with 51% greater odds for diarrhea compared with GLP-1 RA treatment. Tirzepatide use in subjects with type 2 diabetes did not significantly impact the incidence of any serious adverse effects compared with placebo, basal insulin, or GLP-1 RAs [160].

The cardiovascular safety of tirzepatide in type 2 diabetes was demonstrated in a meta-analysis of seven trials and 7,215 subjects randomized to tirzepatide, placebo, or an active comparator. Tirzepatide was associated with a non-significant decrease in the risk for major adverse cardiovascular events (e.g., cardiovascular death, myocardial infarction, stroke, hospitalized unstable angina) and all-cause death [161].

Current evidence suggests that tirzepatide might be more efficacious than GLP-1 RAs in terms of improvements in glycemia, body weight, β-cell function, and insulin sensitivity. Tirzepatide seems at least equally safe as GLP-1 RAs by not increasing the odds for serious adverse events [160].

Results of the ongoing cardiovascular outcome trial (SURPASS-CVOT) are awaited to answer whether tirzepatide exerts cardioprotective effects similar to that observed with GLP-1 RAs. In this trial, tirzepatide is compared with dulaglutide on major cardiovascular events in patients with type 2 diabetes and increased cardiovascular risk. Because dulaglutide has a confirmed cardioprotective effect, this head-to-head study will be particularly informative [160]. The study is expected to conclude in late 2024.

Tirzepatide is known to reduce the efficacy of oral contraceptive medications due to delayed gastric emptying. This delay is largest after the first dose, so patients should switch from oral to nonoral contraceptives for the first four weeks when tirzepatide is initiated [162]. Patients should be counseled regarding the risk of unintended pregnancy and the necessity of other contraceptive methods.

INVESTIGATIONAL ANTIOBESITY MEDICATIONS IN CLINICAL TRIALS

Which investigational antiobesity medication is a triple agonist at GCGR, GIPR, and GLP-1R?

Given the heterogeneity and complex pathogenesis of obesity, combination therapy with multiple pathophysiologic targets is a logical approach to increasing weight-loss response with pharmacotherapy [163]. Peptide engineering, exemplified by tirzepatide, allows the development of multi-receptor agonists [139]. Other antiobesity medications in development include oral GLP-1R mono-agonists. Except where noted, the following agents are administered subcutaneously once weekly.

Cagrilintide

Amylin, a pancreatic hormone released with insulin in response to nutrient intake, acts on:

- Appetitive/energy-regulating hypothalamic neurons impacting food intake
- Dopaminergic neurons in the ventral tegmental area impacting reward and motivation
- Chemoreceptive neurons in the brainstem nucleus tractus solitarius

Pramlintide, the first amylin analog, was approved in 2005 as an adjunct to insulin for type 1 and type 2 diabetes and promotes weight loss in patients with diabetes by substituting three amino acids of human amylin with proline [139; 147]. Cagrilintide is an emerging agent that overcomes pramlintide's short half-life and frequent administration as a long-acting amylin analog. Cagrilintide is being developed in combination with semaglutide (CagriSema) to achieve sustained weight loss in persons with obesity. Both cagrilintide and CagriSema have shown promising weight loss and safety in clinical trials that supports their further development [163].

Among 706 individuals with obesity after 26 weeks, mean weight loss with cagrilintide 4.5 mg (10.6%) and 2.4 mg (9.7%) was greater than with liraglutide 3.0 mg (8.4%) and placebo (2.8%). Side effects of cagrilintide include nausea, diarrhea, constipation, fatigue, and injection-site reactions [147].

CagriSema combines cagrilintide with semaglutide to produce an additive effect on appetite reduction and weight loss [163]. In a trial of adults with obesity, mean weight loss at 20 weeks was 17.1% with CagriSema, compared with 9.8% with semaglutide 2.4 mg [147]. Among 92 adults with type 2 diabetes and BMI ≥27 randomized to once-weekly CagriSema, semaglutide, or cagrilintide (all escalated to 2.4 mg), mean weight loss at week 32 with CagriSema (15.6%) was significantly greater than semaglutide (5.1%) or cagrilintide (8.1%). Mild or moderate gastrointestinal adverse effects were common and comparable. No moderate or greater hypoglycemia was reported [164].

Retatrutide (LY3437943)

A triple agonist may provide even more effective glycemic control and weight loss compared to single or dual receptor agonists. Retatrutide is a triple agonist at GCGR, GIPR, and GLP-1R [139]. A phase 2 dose-response study evaluated retatrutide in 338 adults with obesity [165]. At 48 weeks retatrutide 1 mg, 4 mg, 8 mg, and 12 mg led to 8.7%, 17.1%, 22.8%, and 24.2% mean weight loss, compared with a 2.1% reduction with placebo. Among those who received 8 mg or 12 mg retatrutide, 91% and 93% experienced weight loss ≥10% and 75% and 83% experienced weight loss ≥15% (compared with 9% and 2% among those receiving placebo).

Dose-related mild-to-moderate nausea, diarrhea, vomiting, and constipation were the most common retatrutide adverse effects, partially mitigated with a lower starting dose (2 mg vs 4 mg). Dose-dependent increases in heart rate peaked at 24 weeks and declined thereafter [165; 166].

Survodutide (BI 456906)

Survodutide is a dual GLP-1 and glucagon receptor (GCGR) agonist developed for obesity and NASH treatment. As glucagon release from pancreatic a-cells increases blood glucose, antagonism was initially pursued as a type 2 diabetes treatment. More recent studies have localized GCGR to adipose tissue, brain, and liver and have shown that GCGR activation increased energy expenditure via thermogenesis [139; 147]. An agent combining selectively increased energy expenditure with appetite suppression is a reasonable strategy for effective weight loss or weight maintenance [139]. Hepatocytes express GCGR, but not GLP-1R, and drugs like survodutide that target GCGR may have greater benefit in improving liver fibrosis or NASH than GLP-1RAs [139].

In Phase 1 studies of survodutide, maximum placebo-corrected weight loss was 13.8% after 16 weeks, including 12.37% in Japanese men with no unexpected tolerability concerns [167; 168]. Common survodutide adverse effects included nausea, dyspepsia, vomiting, diarrhea, abdominal pain, and headache [167].

AMG-133

Co-agonism is not the only possible strategy for a unimolecular antiobesity medication. AMG-133 is a GCGR antagonist and GLP-1R agonist [25]. In one study, individuals with obesity averaged 14.3% weight loss after 12 weeks on higher-dose AMG-133. AMG-133 was associated with adverse gastrointestinal effects, but its once-monthly subcutaneous use may be advantageous to weekly tirzepatide [141]. If replicated, the rapidity and extent of this weight loss provokes questions regarding the drug's mode of action and the role of GIP and GLP-1 in physiologic weight regulation [25]. As of 2023, peer-reviewed publication of the full trial results is awaited [141].

Bimagrumab (BYM338)

Bimagrumab is a human monoclonal antibody that binds to the activin type II receptor (ActRII). Antibody blockade of ActRII signaling stimulates skeletal muscle growth, and previous studies suggest that ActRII inhibition with bimagrumab also promotes excess adipose tissue loss and improves insulin resistance [169]. A single intravenous dose of bimagrumab increased lean mass, reduced total body fat mass (by 7.9%), and ameliorated insulin sensitivity in insulin-resistant individuals during the 10-week study [92].

A phase 2 trial randomized adults with obesity and type 2 diabetes to IV bimagrumab (10 mg/kg up to 1,200 mg) or placebo every 4 weeks for 48 weeks. Body composition changes used dual x-ray absorptiometry (DEXA) and magnetic resonance imaging. At week 48, mean changes with bimagrumab vs placebo were noted in fat mass (-20.5% vs -0.5%), lean mass (3.6% vs -0.8%), waist circumference (-9.0 cm vs 0.5 cm), and body weight (-6.5% vs -0.8%) [169]. Muscle spasms and mild diarrhea were the most common adverse effects with bimagrumab. Further studies on the efficacy and safety of bimagrumab are ongoing [92].

Orforglipron (LY3502970)

Orforglipron, an oral once-daily nonpeptide GLP-1 RA, was evaluated in 272 adults randomized to orforglipron (12 mg, 24 mg, 36 mg, or 45 mg) or placebo for 36 weeks [170]. Mean weight loss with orforglipron was 9.4% to 14.7%, compared with 2.3% with placebo. In those taking orforglipron, weight loss ≥10% was noted in 46% to 75%, compared with 9% of patients taking placebo. Orforglipron led to improvement in all prespecified weight-related and cardiometabolic endpoints [170].

The most common orforglipron adverse effects were mild-to-moderate gastrointestinal events, primarily during dose escalation, and led to discontinuation of orforglipron in 10% to 17% of participants across dose cohorts. The safety profile was consistent with GLP-1RAs [170]. This trial mirrored the safety and weight reduction findings of a smaller oral orforglipron trial in patients with type 2 diabetes [171].

Danuglipron

Danuglipron is another oral GLP-1 RA under development for type 2 diabetes and obesity and is taken twice-daily with food [147]. A phase 2b trial randomized 411 adults with type 2 diabetes to placebo or danuglipron. At week 16, mean weight loss difference vs placebo was –2.04 kg and –4.17 kg with danuglipron 80 mg and 120 mg, respectively. The most common adverse effects were nausea, diarrhea, and vomiting. Only 77% of patients completed the trial [172]. In a 12-week, dose-escalation study of adults with type 2 diabetes, discontinuation from danuglipron due to adverse effects ranged from 27.3% to 72.7% [173]. In December 2023, Pfizer halted its trial of twice-daily danuglipron in response to high drop-out rates related to unacceptable side effects; the once-daily trial continued [309].

Ecnoglutide

Ecnoglutide is a novel, long-acting GLP-1 analog being explored for patients with diabetes and obesity. In laboratory tests, ecnoglutide was effective at stimulating the production of cAMP, a key signaling molecule involved in glucose control and body weight regulation. In a phase 1 clinical trial, ecnoglutide was found safe and well-tolerated, with pharmacokinetic properties that support once-weekly subcutaneous injections [174].

In a phase 2 trial of 206 participants with obesity and diabetes, weekly ecnoglutide 1.2 mg, 1.8 mg, or 2.4 mg led to weight loss of 11.5%, 11.2%, and 14.7%, respectively, vs 8.8% with daily liraglutide 3.0 mg [175]. A phase 3 dose comparison trial was initiated in early 2023 [176].

Mazdutide

Mazdutide is a novel once-weekly GLP-1 and glucagon receptor dual agonist. As an oxyntomodulin analogue, mazdutide may also increase energy expenditure and improve hepatic fat metabolism through the activation of glucagon receptor. In a phase 2 trial in China, mazdutide 9 mg led to a mean weight loss of 15.4%, a weight change vs placebo of -14.7 kg, and weight loss ≥20% in 21.7% of participants (vs 0% with placebo) after 24 weeks [177].

APH-012

APHD-012 is a novel approach to address metabolic disease through the delivery of dextrose to the lower small intestines via an oral bead formulation. In the 1960s, researchers found that glucose delivered directly distal to the jejunum better stimulated insulin release and secretion of GLP-1 and GIP compared with glucose delivered higher up the tract. This agent builds on such research [178].

As of 2023, a Phase 2 trial involving 150 adult obese participants with or without endocrine/metabolic conditions is underway [179].

ARD-101

ARD-101 is a potential bitter taste receptor (TAS2R) agonist that stimulates the release of the body's natural CCK, but primarily targets vagal nerve afferents located near the gut; this in turn induces positive effects on hunger, metabolism, and inflammation through gut-brain signaling. Three phase 2 trials were initiated in 2022 to assess efficacy and safety in adults with general obesity, adults with refractory post-bariatric weight gain, and those with Prader-Willi Syndrome, a rare genetic disorder characterized by persistent hyperphagia [180].

In the general obesity trial, patients treated with ARD-101 experienced a 2.51-fold greater reduction in hunger rating vs placebo [181]. Nausea or diarrhea common among available GLP-1 drugs were not noted in the ARD-101 group.

HU6

HU6 has demonstrated inhibition of phosphodiesterase 9A in mice linked to reduced body (and myocardial) fat and stimulated mitochondrial activity, without altered activity levels or food intake [182]. In this trial, positive weight loss effects were exclusively observed in male and ovariectomized female mice, suggesting a strong sexual dimorphism in treatment response. A phase 2 trial initiated in 2023 enrolled 250 participants with type 2 diabetes at risk for NASH and will compare three doses of HU6 on weight loss and hepatic function effects [183].

Nabilone

The endocannabinoid system is involved in the regulation of body weight and metabolism throughout the body. In the CNS, endocannabinoids bind to CB1 receptors in the hypothalamus (which control appetite), gastrointestinal tract, pancreas, and adipose tissue [184]. Elevated endocannabinoid levels can lead to increased hunger and food intake.

However, a meta-analysis of data from the National Epidemiologic Survey on Alcohol and Related Conditions and the National Comorbidity Survey-Replication found a decreased prevalence of obesity among current users of cannabis (≥3 days per week) of 14.3% and 17.2%, respectively [185]. Given this decreased likelihood of obesity in current cannabis users, research has begun to explore how the endocannabinoid system can be manipulated to promote weight loss and improve metabolic health.

Nabilone is an oral synthetic Δ9–THC analog and partial CB1 agonist approved for the treatment of cancer and HIV cachexia for increasing appetite and body weight. A randomized controlled trial of cannabis-naive adults with obesity is underway to examine safety and feasibility, weight-loss effectiveness, changes in gut microbiome, and metabolic markers [186]. The results are expected in 2024–2025.

NNC9204-1177

NNC9204-1177 is a glucagon/GLP-1 receptor co-agonist that underwent three phase 1 trials. After 12 weeks, mean weight loss was 12.6% at the higher dose level. However, dose-dependent increases in heart rate (5–22 beats per minute) and decrease in reticulocyte count, increased markers of inflammation, hepatic disturbances, and impaired glucose tolerance halted further clinical development [187].

CLINICAL USE OF ANTIOBESITY MEDICATIONS

What is the recommended first-line antiobesity medication for obesity management?

If permanent weight loss could be achieved solely with behavioral reductions in food intake and increases in energy expenditure, antiobesity medications would not be needed [120]. Unfortunately, this is not commonly the case. Thus, antiobesity medication pharmacotherapy is indicated as an adjunct to caloric restriction and physical activity in adults with obesity or overweight with weight-related complications [131].

Antiobesity medication approvals have been based on efficacy as adjunctive treatment, including 1960s phentermine trials with 1,000 calorie/day diets for both drug and placebo groups; none have been shown to be effective on their own, because such studies have not been conducted [120; 131; 188]. Patients should be educated that the addition of antiobesity medications to a lifestyle program enhances weight loss, as clinical trials have demonstrated [131]. For example, 224 adults were initiated on sibutramine (discontinued in 2020) and randomized to brief lifestyle counseling or to a comprehensive diet, exercise, and behavior therapy program. At 12 months, mean weight loss with sibutramine plus brief counseling was 4.6% compared with 11.2% among those who received sibutramine plus comprehensive intervention [189].

As of 2023, few professional organizations have independently produced practice recommendations for current antiobesity medication options. In adults for whom antiobesity medications are indicated (per FDA), the 2022 AGA guideline states that long-term pharmacologic therapy is recommended, with multiple effective and safe treatment options that include semaglutide 2.4 mg, liraglutide 3.0 mg, phentermine-topiramate ER, naltrexone-bupropion ER, phentermine, and diethylpropion [123].

Explicit first-choice recommendations have also been made. Data show that greater weight loss (≥10%) leads to greater clinical improvements in weight-related complications, including greater relative risk reduction for cardiovascular events, improvements in NASH histology, decreased disease activity in inflammatory rheumatic disease, and improvements in osteoarthritis, obstructive sleep apnea, and cancer risk [131].

Given the significantly greater weight loss with semaglutide (15%) than other currently approved antiobesity medications (6% to 10%) and with 69% and 50% of subjects attaining weight loss ≥10% and >15%, respectively, semaglutide 2.4 mg weekly is recommended as the first-line antiobesity medication for obesity management [131]. Weight-loss goals for most individuals with obesity should be at least 10% or more, which is now achievable with current antiobesity medications.

After initiating any antiobesity medication, the weight lost by 12 weeks is considered an indicator of treatment response. If adherence can be ensured and 5% weight loss is not achieved after three months, the drug can be given at an increased dose, combined with another drug, stopped altogether, or replaced with a new drug [135].

Nonetheless, long-term pharmacotherapy is still challenged by some who question whether obesity itself constitutes a disease worthy of chronic drug therapy. Lifelong pharmacologic management of chronic diseases such as hypertension might offer a relevant template for obesity treatment strategies. In these diseases, it is common practice to target multiple mechanisms to achieve optimal disease management. It seems inevitable, and with good precedent, that such a conceptual approach to lowering body weight will eventually prevail [132].

Practical Tips for Success with GLP-1 Agonists

When starting GLP-1 agonists, several strategies can promote success and decrease risk of discontinuation. Strategies to minimize adverse effects include slow dose escalation, counseling on expected adverse effects and their duration, and using a multidisciplinary team approach (including the primary care provider, pharmacists, nurses, and medical assistants) to provide regular follow-up and guidance as patients initiate the medication. It is particularly important to discuss gastrointestinal adverse effects, as patients who are not expecting these adverse effects may prematurely discontinue the medication [131].

Routine follow-up can come in many forms, including virtual visits, phone calls, pharmacist check-ins, or even portal messages at routine intervals. This type of follow-up can increase communication with the patient, normalizing expected adverse effects and allowing tighter dose titration, while also reducing the number of clinical visits a patient has to make, thereby reducing primary care provider burden and overall healthcare costs. Other strategies include a dose escalation period, with one-week dose pause when adverse effects are encountered, which may minimize nausea/vomiting. Gastrointestinal adverse effects may also be reduced by avoiding high-fat foods and focusing on small meals [131].

FDA-APPROVED ANTIOBESITY MEDICATIONS AND RETAIL COST, 2023		
Agent	**Typical Maintenance Dose**	**Average Retail Price, 30-Day Supply**
Phentermine	8–37.5 mg daily	$11.31
Diethylpropion	75 mg daily	$48.73
Orlistat	60 mg TID (OTC) 120 mg TID (Rx)	~$45.00 (Alli) $808.06 (Xenical)
Naltrexone/bupropion ER	16/180 mg BID	$308.00
Phentermine/topiramate ER	7.5–15/46–92 mg daily	$231.07
Liraglutide 3.0 mg	Once daily	$1,064.86
Semaglutide 2.4 mg	Once weekly	$1,576.73
Tirzepatide (2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg)	Once weekly	$1,059.87
BID = twice daily, OTC = over the counter, Rx = prescription, TID = three times daily.		
Source: [131]		*Table 8*

Demand and Supply Problems

Interest in GLP-1 RAs has expanded beyond clinicians and patients struggling to lose excessive body-fat mass. Formulations of semaglutide approved for type 2 diabetes (Wegovy and Ozempic) have gained attention as celebrities and social media influencers have described taking thee agents to lose weight in short timeframes [190]. Many people have described in the media how taking semaglutide for obesity fundamentally changed their experience of hunger and appetite [191]. Consumer demand has led to widespread supply shortages of both products and concerns that people will associate them with "vanity," not as critical medications for patients with diabetes with or without obesity [190].

Additionally, news reports have commented on the possible misuse of semaglutide and other GLP-1 analogs. The issue is facilitated by the acquisition of medications from rogue websites. Pharmacists have reported forged prescriptions and use for weight loss in patients without diabetes. Social media influencers' semaglutide promotion for weight-loss, and the associated increase in demand, have contributed to an ongoing worldwide shortage of the drug in 2023 [192].

Off-Label Prescribing of Antiobesity Medications

If all antiobesity medications could be prescribed based on individualized patient need without affordability concerns, discussion of off-label use would not be needed. Unfortunately, medication cost and insurance coverage are the primary drivers in selecting antiobesity medications for an individual patient. In a 2018 review of 136 marketplace health insurance plans, only 11% had coverage for antiobesity medications [193]. Medicare excludes drug therapy for obesity, and only 11 state Medicaid programs have full antiobesity medication coverage (California, Kansas, Minnesota, Wisconsin, Michigan, Pennsylvania, Virginia, Delaware, Rhode Island, Connecticut, and New Hampshire); a limited number of other states may offer partial coverage [131]. Even for patients with insurance, cost can be a barrier due to the lack of antiobesity medication coverage under the diagnosis of obesity [124].

In this context, off-label prescribing includes prescribing an antiobesity medication for longer than its labeled duration [194]. Phentermine as a long-term option is obviously attractive given its low cost (***Table 8***), and there are several considerations to weigh.

The original 90-day label has not been updated since 1959, despite phentermine approval for long-term treatment of obesity when combined with topiramate as Qsymia [124]. Its short-term indication is in conflict with what is now known about the nature of obesity necessitating long-term treatment [195]. When a patient shows good therapeutic response and tolerability with phentermine, the Endocrine Society states this presents a conundrum for clinicians because it is clear that weight regain will likely occur once the medication is stopped [120].

Phentermine has long been the most commonly prescribed antiobesity medication due in large measure to its low potential for CNS stimulation and abuse, its low price as a generic drug, and clinician familiarity [136]. A large proportion has been for off-label doses and durations to sustain a positive clinical response [195].

Authors of the Endocrine Society practice guideline acknowledged little evidence of any serious side effects with long-term phentermine monotherapy and concluded it was reasonable to prescribe it long-term for patients who:

- Lack serious cardiovascular disease and/or serious psychiatric or substance use disorder
- Have been informed about FDA-approved antiobesity medications shown safe and effective for long-term use while phentermine has not
- Do not show clinically significant increases in pulse or blood pressure
- Show significant weight loss on phentermine

These aspects of care should be documented in the patient's medical record, and the off-label nature of the prescribing documented at each visit [120].

Subsequent to this clinical practice guideline, an observational study of 13,972 adults with obesity, including those with hypertension (21%) and type 2 diabetes (12%), initiated on phentermine found no increase in cardiovascular risk with long-term use up to 36 months versus use 3 months of less [196].

An obesity medicine specialty clinic also examined the abuse liability of phentermine treatment in 269 patients administered validated, structured addiction medicine interviews. No evidence was found of compulsive use, cravings, unsanctioned dose escalation, or withdrawal symptoms on abrupt cessation, including at doses much higher than commonly recommended and after treatment durations of up to 21 years [197].

The AGA and the ASMBS recommend phentermine as a long-term antiobesity medication option. The OMA convened a roundtable discussion of phentermine by expert clinicians, who suggested that, while not required by the prescribing label, prescribers may obtain an electrocardiogram (ECG) before starting phentermine. In addition to finding troubling wave patterns or cardiac dysrhythmias, a baseline ECG helps bring piece-of-mind to patient and clinician. Some clinicians perform ECGs on all patients before any intensive weight loss program or antiobesity medication [198]. In addition, the experts state that phentermine can be combined with GLP-1 RAs or other antidiabetic drug classes for further weight reduction, especially in patients with a high burden of obesity. Phentermine should not be used in patients with active cardiovascular disease nor as first-line antiobesity medication with advanced age or cardiovascular disease risk factors. Patients with a history of methamphetamine use are best treated with DEA unscheduled, non-stimulant antiobesity medications or bariatric procedures [198].

It is important to pick the right drug for the right patient. A patient who tends to skip meals all day and eat large volumes late at night might not be a good match for morning phentermine, which would mainly reduce daytime hunger. If phentermine is prescribed, patients should be advised that they may have trouble sleeping for two to three nights after initiating phentermine [198].

Canagliflozin is an SGLT2 inhibitor approved for type 2 diabetes. In a randomized controlled trial of 335 subjects without type 2 diabetes (mean BMI: 37.3), the weight loss effects of once-daily canagliflozin 300 mg (Cana), phentermine 15 mg (Phen), or combined Cana/Phen were compared after 26 weeks [199]. Mean weight loss with placebo, Cana, Phen, and Cana/Phen was 1.1%, 2.6%, 4.6%, and 8.1%, respectively. Weight loss with Cana/Phen continued through week 26, with no apparent plateau. The Cana/Phen group also had greater improvements in blood pressure and heart rate. This study demonstrated the complementary renal effects with canagliflozin and CNS activity with phentermine on weight loss [199].

In commenting about the cost barrier of phentermine/topiramate ER, some have suggested prescribing phentermine and generic topiramate separately at monotherapy dosages that match Qsymia to lower the cost, noting that topiramate is not approved as an antiobesity medication but has shown benefits against weight regain following bariatric surgery [150].

Low-cost, off-label prescribing has focused on phentermine due to its extensive familiarity to obesity specialists, but diethylpropion also has low cost, comparable benefit and safety as monotherapy, and is likewise endorsed as a long-term antiobesity medication option by the AGA [123].

BARIATRIC SURGICAL PROCEDURES AND DEVICES

Bariatric approaches encompass invasive laparoscopic surgical procedures, minimally invasive endoscopic therapies that remodel the stomach using suturing/plication devices or that insert space-occupying devices to reduce gastric volume, and endoscopically placed vagal stimulation devices [125].

As discussed, the hazards of obesity are many, including a shortened life span, type 2 diabetes, cardiovascular disease, some cancers, kidney disease, obstructive sleep apnea, gout, osteoarthritis, and hepatobiliary disease, among others. Weight loss reduces all of these diseases in a dose-related manner—the more weight lost, the better the outcome [4]. Bariatric surgery is the most effective treatment for severe obesity and obesity with metabolic disease. In the majority of appropriately selected cases, substantial weight loss is sustained for years if not decades [200].

ASMBS-ENDORSED SURGICAL APPROACHES			
Procedure	**Optimally Suited For**	**Percent Excess Weight Loss[a]**	
		At 2 years	At 10 years
Roux-en-Y gastric bypass (RYGB)	Higher BMI, GERD, diabetes	55% to 75%	52% to 69%
Sleeve gastrectomy	Metabolic disease	50% to 70%	67% to 71%
Laparoscopic adjustable gastric banding (LAGB)	Lower BMI, no metabolic disease	30% to 50%	38% to 47%
Biliopancreatic diversion with duodenal switch (BPD/DS)	Super-obesity (BMI ≥50), diabetes	63% to 80+%	68%
Single anastomosis duodenal-ileal bypass with sleeve (SADI-S)	Super-obesity	74%	NA
One-anastomosis gastric bypass (OAGB)	Higher BMI, diabetes	68% to 80%	73%
BMI = body mass index, GERD = gastroesophageal reflux disease, NA = not available. [a]Mean average.			
Source: [127; 135; 202; 203]			*Table 9*

The ASMBS, the largest professional organization and recognized authority and resource on metabolic and bariatric surgery, has endorsed six surgical approaches for obesity (***Table 9***) [201]. None involve devices.

Bariatric operations increased from 158,000 in 2011 to 263,000 in 2021, including sleeve gastrectomy (153,000), Roux-en-Y gastric bypass (RYGB) (56,500), revisional (31,000), biliopancreatic diversion with duodenal switch (BPD/DS) (5,525), gastric balloon (4,100), endoscopic sleeve gastroplasty (ESG) (2,200), one-anastomosis gastric bypass (OAGB) (1,149), and single anastomosis duodenal-ileal bypass with sleeve (SADI-S) (1,025) [201].

RYGB is the prototypical bariatric surgery in use for many decades. Restrictive procedures (e.g., LAGB, vertical banded gastroplasty [VGB]) were widely used in the 1980s and 1990s as simpler alternatives to RYGB with fewer complications [204]. With malabsorption thought necessary for effective weight loss, BPD/DS was introduced as a two-stage procedure, initiated with sleeve gastrectomy. Large weight loss during sleeve gastrectomy led to its stand-alone use after 2008 and progressive replacement of VGB and LAGB [204; 205]. LAGB fell from 56,000 procedures in 2011 to just 1,121 in 2021 [201].

TERMINOLOGY

Some terminology in the bariatric literature differs from or seldom appears in the antiobesity medication literature. This includes [4; 119]:

- Metabolic and bariatric surgery (MBS): This is often preferred to the term "bariatric surgery," because these procedures are superior to intensive medical treatment for controlling and inducing remission of type 2 diabetes.
- Obesity-related complications: Replaces the term "weight-related complications," because patients with BMI <30 have not traditionally been considered MBS candidates.
- Pre-operative: The preferred term (rather than baseline) when referring to condition prior to MBS. May be notated with a p prefix (e.g., pBMI, pT2DM).

In discussion of MBS outcomes, those occurring in the 1 to 2 years following the procedure are considered short-term; medium-term outcomes are seen after 3 to 10 years, and those seen more than 10 years after surgery are considered long-term [206].

Percent excess weight loss is a more common measure of impact than percent weight loss. Excess weight is total weight above an ideal reference standard, usually BMI 25. Percent excess BMI loss uses the same concept in units of BMI. For example, in a study of 846 patients (average pBMI: 50.0) treated with RYGB, the outcomes (mean) after one year [207]:

- BMI: 33
- BMI units lost: 17
- Percent excess BMI loss: 68%
- Post-RYGB weight: 204 pounds
- Absolute weight lost: 106 pounds
- Percent weight loss: 34%
- Percent excess weight loss: 72%

Thus, for the same amount of weight loss in the same patients, percent of excess weight loss was about twice that of overall weight loss [127].

PROPOSED MECHANISMS

Considering that similar weight loss via caloric restriction provokes powerful adaptive and counter-regulatory responses (e.g., increased hunger, reduced metabolism), the sustained weight loss effects and diminished adaptive responses after MBS have sought explanation [200]. More recently, the long-term metabolic improvements have attracted investigation.

MBS is traditionally classified as restrictive, malabsorptive, or restrictive plus malabsorptive (e.g., BPD/DS) [208]. Historically, macronutrient malabsorption and restriction were considered necessary for efficacy [200; 209]. However, RYGB and sleeve gastrectomy produce large and sustained weight loss despite lower malabsorption. The weight-loss efficacy of both likely involve normal physiological mechanisms affecting energy intake, expenditure, and metabolic regulation, significantly mediated by increased GLP-1 signaling and also by melanocortin signaling pathways, which clearly go beyond mechanical restriction and malabsorption [200].

Bypassing the duodenum via RYGB is thought to uniquely benefit metabolic parameters, independent of weight loss [210]. However, an 18% weight loss with RYGB or caloric restriction showed similar metabolic benefits due to the weight loss itself in patients with obesity and type 2 diabetes [211]. Patients attained similar type 2 diabetes remission rates after RYGB (72%) and sleeve gastrectomy (70%) in a study that established a weight-loss threshold of ≥20% for type 2 diabetes remission [212].

Thus, type 2 diabetes mitigation is dependent on weight loss and appears independent of MBS approach, although the literature is inconsistent and the underlying mechanisms of efficacy remain unclear [209]. Some inconsistency stems from retrospective versus prospective data and short-term versus long-term follow-up.

More broadly, greater clinician and patient acceptance of MBS is believed to hinge on more rigorous evidence of weight loss durability and obesity-related complication amelioration from prospective, long-term data. This includes ≥80% patient follow-up [206; 213]. However, the history of MBS shows frequent innovations, technical progress, and implementation of new approaches. The longer the timeframe of patient accrual or follow-up, the greater the odds that the procedure has been modified or replaced [214].

INDICATIONS FOR BARIATRIC SURGERY

The universally applied threshold for bariatric surgery (i.e., BMI >40 or BMI >35 with comorbidities) was set in 1991 by the National Institutes of Health. With significant advances in obesity science and safer, more effective bariatric approaches supported by three decades of evidence, this indication no longer reflects best practice and was replaced with new practice guidelines by the ASMBS in 2022 [126]. According to the ASMBS, MBS is recommended for [126]:

- Patients with BMI ≥35, regardless of presence, absence, or severity of obesity-related complication
- Patients with type 2 diabetes and BMI ≥30

MBS should also be considered in patients with BMI 30–35 who do not achieve substantial or durable weight loss or obesity-related complication improvement nonsurgically [126].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society of Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders assert that metabolic and bariatric surgery is recommended for individuals with a BMI >35 kg/m^2, regardless of presence, absence, or severity of comorbidities.

(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9834364. Last accessed November 28, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

The BMI thresholds should be adjusted in Asian populations [126]. A BMI >25 suggests clinical obesity in these patients, and those with BMI >27.5 should be offered MBS.

The ABMS asserts that there is no upper age limit to MBS [126]. Older patients who could benefit from MBS should be considered after careful assessment of comorbidities and frailty.

MBS is also an effective treatment of clinically severe obesity in patients who need other specialty surgery, such as joint arthroplasty, abdominal wall hernia repair, or organ transplantation. Severe obesity is a chronic disease requiring long-term management after primary MBS, which may include revisional surgery or adjuvant antiobesity medication to achieve or sustain desired treatment effects [126].

PRE- AND POSTPROCEDURE ECOMMENDATIONS

Although safety is a concern with MBS, perioperative mortality rates (0.03% to 0.2%) have substantially improved from the early 2000s [215]. Studies consistently report that surgeon and surgical center experience are predictors of safety [4].

The OMA recommends that MBS procedures be performed at surgery centers with accreditation for quality standardization, such as the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP) administered by the ASMBS and the American College of Surgeons [127]. A multidisciplinary team can help manage the patient's modifiable risk factors to reduce perioperative complications and improve long-term outcomes [126].

Preprocedure Evaluation and Medical Clearance for Bariatric Procedures

Before undergoing bariatric surgery, a preoperative medical evaluation is optimally conducted by an obesity specialist. A bariatric surgery specialist consultation should also be performed, as well as cardiology, pulmonary, gastroenterology, and/or other specialists, as clinically indicated [127].

Potential MBS candidates should undergo a formal mental health evaluation by a qualified licensed professional to assess environmental, familial, and behavioral factors, including trauma history, suicide risk, coping mechanisms, and underlying eating, mood, and substance use disorders. Patients should receive education regarding the potential for increased suicide risk and addiction postprocedure. After RYGB and sleeve gastrectomy, high-risk groups should stop drinking due to postoperative impaired alcohol metabolism and increased risk of alcohol use disorder [125; 127].

Patients should undergo nutritional assessments by registered dietitians with expertise in MBS, who can help obtain a comprehensive weight history, identify maladaptive eating behaviors or patterns, and correct any micronutrient deficiencies prior to surgery. A registered dietitian can also provide preoperative nutrition education and prepare the patient for expected dietary changes after MBS, which include an understanding that even with bariatric surgery, lifelong adherence to healthful nutrition, physical activity, and favorable behavior modification facilitates the best chance for long-term success [127].

Other preoperative evaluations include proactive medication adjustment. While individual instructions will vary depending on the individual patient, several weeks prior to the bariatric surgery, the medical and surgical team often work together in management of medications that may increase surgical risk, such as increased bleeding risk with antiplatelet therapies (e.g., clopidogrel), anticoagulants (e.g., warfarin), and increased thrombotic risk with sex hormone pharmacotherapies (e.g., estrogens). All herbal and over-the-counter supplements should be discontinued [127].

NSAIDs should be avoided before and after MBS, because they are implicated in the development of anastomotic ulcerations, perforations, and leaks. Alternative pain medication should be identified before the surgery [125].

Tobacco use, and cigarette smoking in particular, must be avoided at all times by all patients. Patients who smoke cigarettes should stop as early as possible, preferably one year but at the very least six weeks before MBS. In addition, tobacco use must be avoided post-MBS given the increased risk of poor wound healing, anastomotic ulcer, and overall impaired health. Structured intensive smoking cessation programs are preferable to general advice and should be implemented [125].

Postoperative Nutritional Considerations

Nutrient deficiencies are common after bariatric surgery and are carefully monitored for optimal patient health and recovery. Lower levels of vitamin D are common in patients with obesity and may worsen postoperatively without adequate supplementation. High-quality bariatric-specific multivitamin/mineral/trace element supplements are routinely recommended after MBS, with vitamin supplements often containing higher amounts of vitamin B12, iron, vitamin C (to assist with iron absorption), vitamin D, and calcium [127]. Registered dietitians can also assist postoperative patients experiencing food intolerances, malabsorption issues, micronutrient deficiencies, or weight regain [126].

Procedure Selection

Selection should be based on individualized goals of therapy (e.g., weight-loss target, improvements in specific obesity-related complication), available local/regional expertise (e.g., obesity specialists, bariatric surgeon, institution), patient preferences, and personalized risk stratification that prioritizes safety. Laparoscopic should be preferred over open procedures [125]. The decision about MBS approach should be driven primarily by informed patient preferences, but the ultimate decision for surgical readiness will be determined by the surgeon [126; 215].

Other Issues

Preoperative Predictors of Outcome

Because weight loss after surgery is heterogeneous and not entirely predictable, particularly in the long-term, there is considerable interest in identifying individuals more or less likely to benefit from MBS based on preoperative factors [208]. Although age, gender, anthropometrics, obesity-related complications, eating behavior, genetic background, circulating biomarkers (e.g., microRNAs, metabolites, hormones), and psychological and socioeconomic factors could potentially impact post-MBS weight loss, none have shown predictive utility [216].

A study of 2,022 patients with average three-year weight loss of 31% with RYGB and 16% with LAGB concluded that preoperative factors have limited predictive value for a patient's chance of a successful weight loss outcome following MBS [217]. However, surgical volume at the clinic (more than 100 per year), surgeon experience, surgery in a tertiary care center, female sex, age 55 years or older, and respiratory status all correlated with lower complications risk [208].

As genetic variants in the leptin-melanocortin pathway are associated with obesity, their effect on long-term bariatric outcomes was examined. The weight regain pattern in these patients after RYGB and sleeve gastrectomy highlights the need for proactive lifelong management to prevent relapse and careful expectation management [218]. Additionally, genotyping patients with significant weight regain after RYGB could help individualize weight-loss interventions to improve weight maintenance after surgery [219].

Preoperative Denials or Delays of Approval for Insurance Coverage

Insurance-mandated preoperative weight loss is discriminatory, arbitrary, scientifically unfounded, and contributes to patient attrition, or worse [126]. In a large study of patients medically cleared for a bariatric procedure and for whom insurance approval was requested, 22% were denied insurance coverage. For these patients, the mortality rate increased threefold during follow-up [220]. This practice by insurers leads to unnecessary delay of life-saving treatment and progression of life-threatening comorbid conditions [126].

Postoperative Esthetic Concerns

Bariatric surgery (and possibly antiobesity medication in hyperresponders) can lead to massive weight loss, resulting in excess skin and tissue that impairs hygiene, causes discomfort, and is disfiguring. Excess skin can lead to stigma due to appearance and pronounced physical and psychological impairments, but it can be mitigated by body-contouring surgery [221]. Body-contouring surgery is best pursued after weight loss has stabilized (typically 12 to 18 months after bariatric surgery) [125]. Smoking cessation is an absolute requirement before any type of body-contouring surgery [221].

Abdominoplasty can improve mobility, reduce skin fold complications, and improve psychosocial functioning. Patients who underwent body-contouring surgery after bariatric surgery had significantly better long-term weight loss than a matched cohort of patients [222]. A subsequent meta-analysis confirmed the added long-term benefits of body-contouring surgery for selected patients after massive weight loss and recommended a multidisciplinary team involving a bariatric surgeon, a plastic surgeon, nutritionists, and psychologists for the management of patients [223].

SURGICAL APPROACHES

What is the criterion-standard MBS with the longest-term safety and efficacy data?

There are several measures of procedure success. Nadir weight loss is defined as the lowest weight post-MBS, while weight recurrence is the weight regained after nadir. A case is categorized a nonresponse if the nadir excess weight loss is <50% of pre-MBS excess weight. Interventions for nonresponse and weight recurrence include revision or conversion (to another MBS type), corrective (to resolve a complication), and antiobesity medication augmentation [125; 224].

Weight-loss success with MBS has often been defined as ≥50% excess weight loss and/or ≥25% total weight loss [212]. In the first validation of success criteria for MBS, ≥25% total weight loss exceeded 90% [225]. The quality of evidence for surgical bariatric approaches continues improving, with more prospective and longer-duration results, comparisons between MBS, and systematic reviews and meta-analyses.

Roux-en-Y Gastric Bypass (RYGB)

RYGB is the criterion-standard MBS with the longest-term safety and efficacy data [226]. In this procedure, the stomach is divided; a small gastric pouch is anastomosed (cross-connected) to a severed "roux" limb of small bowel jejunum through which food passes, bypassing the larger gastric remnant, duodenum, and proximal jejunum [227]. This approach has been found to dramatically improve type 2 diabetes and is part of the treatment algorithm for uncontrolled type 2 diabetes in patients with BMI ≥35. It is also associated with modestly greater weight loss and improvements in metabolic disease compared with sleeve gastrectomy. It also improves GERD [127; 135].

However, it is associated with more malabsorptive complications than sleeve gastrectomy, though fewer than duodenal switch. The bypassed portion of stomach cannot be viewed by conventional gastroscopy; if cancer occurs after surgery, early diagnosis is almost impossible [228]. RYGB is also not recommended for patients with Crohn disease. Potential adverse effects include marginal ulcers, internal hernia, small bowel obstruction, and vitamin and mineral deficiencies.

Efficacy

A prospective study followed 486 patients after RYGB. Average total weight loss at 2 years (36%) and 15 years (28%) showed good durability. Rates of improved or resolved obesity-related complication after one year for type 2 diabetes (99%), obstructive sleep apnea (97%), hypertension (95%), and GERD (97%) remained high through ≥10 years [226].

After RYGB, 418 patients were prospectively studied (with >90% follow-up) at 12-years. Mean total weight loss was 28.0% at 6 years and 26.9% at 12 years. Approximately 70% and 40% of patients maintained ≥20% and ≥30% total weight loss. Type 2 diabetes remission at 2, 6, and 12 years was 75%, 62%, and 51%, respectively; prevention of new-onset type 2 diabetes was 98% [229]. Evidence suggests that RYGB provides stable weight loss of more than 25% beyond 12 to 15 years that corresponds with sustainable resolution of obesity-related complications.

Sleeve Gastrectomy

Sleeve gastrectomy, also referred to as laparoscopic sleeve gastrectomy or LSG, consists of the majority of the stomach being vertically resected; a tube-shaped remnant, or "gastric sleeve," is left along the lesser curvature [227]. This procedure improves metabolic disease while maintaining small intestinal anatomy. Due to its effectiveness, relative simplicity, and low rates of margin bleeding (1.0%), leakage (1.1%), and postoperative stenosis (0.4%), sleeve gastrectomy has become the most popular MBS [228]. Micronutrient deficiencies not as frequent with sleeve gastrectomy as with some other bariatric surgeries. If necessary, these patients can be converted to RYGB at a later stage.

Despite the benefits, rates of GERD and dysphagia are high. In some cases, these effects may be severe, requiring conversion to RYGB and/or chronic medical therapy (e.g., with proton pump inhibitors) [127; 135]. Lack of bypass makes sleeve gastrectomy suboptimal for improving obesity-related complications in superobesity; other drawbacks include weight recurrence and poor diabetes control [228]. Chronic obstructive symptoms and potential strictures are additional concerns.

Efficacy

There has been concern that the popularity of sleeve gastrectomy has outpaced its long-term evidence support, especially in superseding RYGB. A systematic reviews and meta-analyses of ≥10-year sleeve gastrectomy results found 24.4% total weight loss and good remission of type 2 diabetes (45.6%) and hypertension (41.4%). However, high de novo GERD (32.3%) and 0% diabetes remission were noted in two of the reviewed studies [230].

In a randomized trial involving 240 patients with 85% follow-up at 10 years, sleeve gastrectomy led to 43.5% excess weight loss (vs 51% with RYGB), <5% weight loss in 5% of participants (vs 3% with RYGB), and similar remission of type 2 diabetes (26% vs 33%), dyslipidemia (19% vs 35%), and obstructive sleep apnea (16% vs 31%). Superior hypertension remission was noted with RYGB (8% vs 24%). The researchers found higher esophagitis rates after sleeve gastrectomy (31% vs 7%) but similar Barrett esophagus (4% vs 4%) and reoperation (15.7% vs 18.5%) rates. Longer preoperative type 2 diabetes duration was associated with lower remission, emphasizing the importance of early surgical treatment [231].

Laparoscopic Adjustable Gastric Banding (LAGB)

In LAGB, an adjustable silicone band is placed around the upper stomach and connected to a port in the subcutaneous tissue, which can be used to restrict the food-holding capacity of the stomach [127; 135]. LAGB is the considered safest bariatric surgical procedure, and it is reversible if necessary [203]. Today, LAGB is disfavored due to lack of durable long-term weight loss, limited metabolic benefits, and the risks of device complications and revisional surgery [127; 135].

Possible adverse events include band slippage, erosion, bowel obstruction, and dilatation of the esophagus. Band overfilling may underlie some LAGB problems. In one study, among 699 LAGB patients (pBMI: 41.4) with low (≤3 mL) or high (≥4 mL) band filling, low filling led to superior BMI (30.3 vs 35.8) and excess weight loss (49.1% vs 38.2%) at four to six years, and substantially lower rates of vomiting, epigastric pain, reflux, band slippage, migration, removal, and revision compared with high filling. Using low-volume band filling and strict follow-up, the authors suggest that abandonment of LAGB should be reconsidered [232].

Efficacy

Following LAGB, excess weight loss at 10 to 20 years is approximately 47%. However, the distribution of weight loss is heterogeneous. At seven years, 62% of patients have 15% total weight loss, and equal rates have ≥35% (19%) and <5% (19%) total weight loss [233].

Due to late complications, de novo GERD in up to 70% of patients, and comparatively mediocre long-term effectiveness, trends over the past decade indicate that LAGB is managed in patients treated years or decades earlier, rather than initiated as MBS [201; 233].

Biliopancreatic Diversion with Duodenal Switch (BPD/DS)

BPD/DS involves sleeve gastrectomy, transection of the duodenum distal to the pylorus, and creation of an alimentary limb 200–250 cm long, thereby reducing anastomotic ulcers and dumping syndrome [228]. This approach is associated with the highest weight loss and metabolic disease resolution of all MBS techniques.

Technical complexity and risk of long-term nutritional deficiencies limits the acceptance of BPD/DS, which is reserved for super-obese (BMI ≥50) patients or those with nonresponse after sleeve gastrectomy without GERD, with nadir excess weight loss of 70% to 80% after two years [200; 228; 234]. Patient unwillingness or inability to follow/afford long-term nutritional recommendations, which can lead to life-threatening micronutrient deficiencies, is considered an absolute contraindication to this approach [127; 135]. Other possible adverse effects include protein malnutrition, anemia, diarrhea, stomach ulceration, duodenal dissection, and internal hernias.

Efficacy

As RYGB can lead to insufficient weight loss in patients with super-obesity (BMI >50), some surgeons advocate BPD/DS in this group [132]. In a study involving 47 patients (pBMI: 54.5) randomized to BPD/DS or RYGB (81% with 15-year follow-up), 1-, 3-, and 15-year BMI was superior with BPD/DS (28, 31, 34) compared with patients who had undergone RYGB (33, 39, 41), reflecting 20.4 vs 12.4 BMI loss and 37.5% vs 23% total weight loss [132].

Unfortunately, BPD/DS also led to greater adverse events (2.7 vs 0.9 per patient), GERD (22.2% vs 0%), and severe adverse effects (0.9 vs 0.3 per patient), including malnutrition and bowel perforation. Long-term mortality did not differ. The trial was not powered for significant differences in obesity-related complication remission.

That half of patients with RYGB remained severely obese is greatly concerning, as BMI >40 reduces life expectancy by 8 to 10 years. The benefits of BPD/DS should be weighed against the increased risk of complications, which may be severe, and the need for rigorous follow-up. However, weight and comorbidity recurrences are problematic, creating health consequences and reducing life expectancy [132].

Single-Anastomosis Duodenal-Ileal Bypass with Sleeve Gastrectomy (SADI-S)

SADI-S creates a single, end-to-side anastomosis between the created gastric sleeve pouch with preserved pylorus and distal ileum, with the division at the level of the duodenum [135]. This approach was introduced in 2010 as a simplified version of BPD/DS and is characterized by strong metabolic effects. Short-term outcomes appear similar to BPD/DS in measure of excess weight loss (BPD/DS: 81%; SADI-S: 75%), improvement of obesity-related conditions, malnutrition, and complications [228]. Potential drawbacks include micronutrient deficiencies and duodenal dissection.

Efficacy

In one study, 121 patients (pBMI: 52) had BMI ≤29, excess weight loss 80%, and total weight loss 57% after 31 months. Post-30-day adverse events (3.3%) were malnutrition or chronic diarrhea [235]. A SADI-S review noted little weight regain after 24 months, resolution of type 2 diabetes (73%), dyslipidemia (77%), and hypertension (59%) [236].

In another study, three-year total weight loss was superior with SADI-S (39%) compared with RYGB (29%). Weight loss with RYGB (30%), SADI-S (35.5%), and BPD/DS (35%) was similar in obesity with type 2 diabetes. Diabetes improved comparably with SADI-S and BPD/DS and better than RYGB [234]. For unclear reasons, longer-duration data on SADI-S are lacking.

One-Anastomosis Gastric Bypass (OAGB)

OAGB was introduced as a simplified version of RYGB, with a significantly reduced difficulty, learning curve, and operation time [228]. It consists of a single gastrojejunal anastomosis between a long gastric pouch and a jejunal omega loop [228]. It may be simpler and safer than BPD/DS, with strong metabolic effects. It may also have less micronutrient deficiencies than BPD/DS.

OAGB is suitable in patients who are elderly, with low BMI (30–35) and obesity-related complications, and high BMI (>50) as one-stage procedure. It may also be suitable for patients with large/concurrent hiatal hernia [202].

This procedure is not reversible and is not recommended for patients with GERD or esophagitis [125]. Potential adverse effects include abdominal pain, nausea, liver abscess, micronutrient deficiencies, and duodenal dissection.

Efficacy

OAGB showed substantial, durable weight loss in a trial involving 1,200 patients (pBMI: 46), with 6-, 9-, and 12-year BMI (28.5, 29.6, 29.9), excess BMI loss (83%, 78%, 76%), and excess weight loss (77%, 72%, 70%) all showing improvement. Approximately 70% of patients had data at 12 years [237]. Patients showed remission of presurgery type 2 diabetes (94%), insulin resistance (100%), hypertension (94%), hyperlipidemia (96%), GERD (92%), obstructive sleep apnea (90%), respiratory insufficiency (100%), and fatty liver (100%). In addition, improvement/remission was noted in osteoarthritis (82%/18%) and urinary incontinence (78%/22%). All affected patients experienced improvement in polycystic ovarian disease. Complications included early severe events (2.7%), late severe events (1%), and bile reflux symptoms (2%). No followed patient required conversion for weight regain [237].

ENDOSCOPIC BARIATRIC TECHNIQUES

Which intragastric balloon devices are ASMBS-endorsed and FDA-approved for six-month dwelltime?

Endoscopic bariatric therapies have emerged as minimally invasive alternatives for patients who are not surgical candidates or who do not want to undergo surgical intervention. These approaches are expected to eventually fill the gap between conservative treatment and surgical bariatric procedures [228]. However, long-term data are needed to determine the durability of safety and efficacy.

Endoscopic Sleeve Gastroplasty (ESG)

ESG reduces gastric volume by 70% to 80%, creating a narrowed luminal sleeve—similar to sleeve gastrectomy, but without incisions or laparoscopy—using an endoscopic suturing device (OverStitch, Apollo Endosurgery, Austin, TX, USA) [238; 239]. It is approved by the FDA for patients with BMI 30–50 [238]. It acts via gastric remodeling that increases PYY and GLP-1 by decreasing leptin and preventing rising ghrelin release, which increases fullness, decreases hunger, and promotes greater weight loss [238].

ESG is associated with fewer adverse effects than other bariatric procedures, with no obvious disadvantages [239]. The most common possible adverse effects include postprocedure nausea, vomiting, and epigastric pain. Severe adverse effects are rare (0% to 2%) [228; 238].

In one study, 6-month weight loss robustly predicted 24-month weight loss, allowing early prediction of nonresponse and initiation of adjunctive therapies [238]. The MERIT trial randomized 209 participants to lifestyle modification with or without ESG. At 52 weeks, ESG showed superior excess weight loss (49% compared with 3%) and weight loss (14% compared with 0.8%) to controls. At 104 weeks, 68% of patients with ESG maintained ≥25% excess weight loss. No deaths, surgical interventions, or intensive care stays occurred [240].

In the longest prospective outcomes, weight loss at three and five years was 15% and 16%, respectively [228]. In 404 adults (pBMI: ≥40) after three years, weight loss was 20.3% and excess weight loss was 47% [62]. A meta-analysis of studies assessing efficacy of ESG found short-term and medium-term weight loss of 16.2% and 15.4%, respectively, and resolution of type 2 diabetes (55%), hypertension (63%), dyslipidemia (56%), and obstructive sleep apnea (52%) in patients with moderate obesity [241].

A study of ESG in 189 overweight patients (pBMI: 28) showed weight loss at 12, 24, and 36 months of 15%, 15.3%, and 15%, respectively. At 12 and 24 months, 76% and 86% of participants achieved normal BMI, with mean BMI reductions of 4.1 and 4.3. ESG was safe and effective in treating overweight patients, with high BMI normalization rates that could halt progression to obesity [242].

Overall, ESG looks promising as a minimally invasive bariatric procedure but needs longer-term data.

Laparoscopic Gastric Plication

Laparoscopic gastric plication is also referred to as a primary obesity surgery endoluminal (POSE) procedure. This incisionless procedure creates full-thickness plications in the gastric fundus and body using anchors that effectively reduce gastric capacity. Whereas endoscopic suturing is somewhat reversible, laparoscopic gastric plication places polypropylene anchors with baskets cinched on either end of tissue folds and is designed for permanent gastric remodeling. To accomplish this, it uses the incisionless operating platform, a medical device. As with ESG, laparoscopic gastric plication is associated with fewer adverse events compared with other bariatric procedures. The most common complaints are abdominal pain, nausea, and vomiting [127; 135; 239].

In a meta-analysis of the original laparoscopic gastric plication procedure, excess weight loss was 49% and weight loss 13% at 12 to 15 months. Severe adverse events occurred in 3% of cases and included bleeding, hepatic abscess, severe pain, nausea, and vomiting [243].

Laparoscopic gastric plication outcomes after five or more years are scarce. Among 88 patients at two and six years, weight loss was 21% and 12% and excess weight loss was 60% and 32%. The six-year weight regain of 58% led to a high revision rate (23.5%) [244].

Intragastric Balloon Devices

Intragastric balloon devices are filled with liquid or gas to reduce the effective volume of the stomach, thereby lowering the satiety threshold of meals, stimulating gut chemo-motor receptors, regulating ghrelin and other peptide hormone levels, reducing food intake, and delaying stomach emptying to achieve weight loss [228].

Three intragastric balloon devices are ASMBS-endorsed and FDA-approved for six-month dwell-time. The Orbera and Reshape balloons are both filled with methylene blue and saline. A leak or rupture releases the dye, which turns the urine blue to rapidly reveal the problem [135; 228].

Contraindications to intragastric balloon devices use include prior abdominal or weight-reduction surgery, inflammatory bowel disease, obstructive disorders, GI ulcers, severe reflux, prior GI bleeding, severe liver disease, coagulopathy, ongoing alcohol use disorder, or intestinal varices, stricture, or stenosis [239; 245].

Orbera Balloon Device

Orbera, the most widely and longest used intragastric balloon device, is an endoscopically inserted single gastric balloon filled with 400–750 mL of fluid [245]. In a meta-analysis of 1,683 patients, weight loss at 6 and 12 months was 13.2% and 11.3%, respectively. Common adverse events were pain (34%), nausea (29%), GERD (18%), gastric mucosal erosion (12%), and balloon removal due to intolerability (7.5%). Severe events included gastric ulcers (2.0%), balloon displacement (1.4%), small bowel obstruction (0.3%), perforation (0.1%), and death (0.08%). All perforations occurred in patients with prior gastric surgery; all deaths were secondary to perforation or aspiration. Thus, individualized, detailed risk assessment is necessary for patients planning to undergo intragastric balloon device placement [228]. Orbera early removal is also associated with use of selective serotonin or serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs) [125].

Obalon Balloon System

Obalon uses up to three deflated balloons, swallowed as capsules. Gas is then injected into the balloons under x-ray observation. Weight loss typically is about 6.6%. In a registry of 1,343 patients, weight loss was 10.0% in the indicated BMI category (BMI 30–40), 10.3% in BMI 25–30, and 9.3% in BMI >40. Adverse event (14%) and severe adverse event (0.15%) rates included seven balloon deflations, none of which resulted in obstruction [246].

Common adverse effects are mainly nausea and mild abdominal pain, and serious events are rare. However, leaking occurs more easily with gas-filled than liquid-filled balloons, and leaking balloons must be removed by gastroscopy, a disadvantage with Obalon [228; 245].

ReShape Duo Balloon

With the ReShape Duo balloon device, two balloons are connected by a soft silicone rod. Each balloon is filled with 450 mL of fluid. The two-balloon design is intended to prevent premature failure, better conform to the stomach curvature, and improve patient tolerability. The ReShape device significantly reduces severe adverse effects rates compared with Orbera, but postoperative adverse event rates remain relatively high [228]. Average weight loss is approximately 6.8% [135].

AspireAssist

AspireAssist was a form of aspiration therapy via modified percutaneous endoscopic gastrostomy. In 2022, the maker of AspireAssist terminated production of this FDA-approved product [247].

OTHER OPTIONS

The TransPyloric Shuttle (TPS)

In 2019, the FDA approved the TransPyloric Shuttle (TPS) to promote weight loss in patients with BMIs 30–40 for a dwell time of 12 months. TPS provides a mechanism similar to intragastric balloon devices, with easy reversibility. The device contains a space-occupying balloon and a flexible silicone catheter that connects to a smaller bulb designed to intermittently advance through the pylorus to induce gastric outlet obstruction [239].

The initial TPS feasibility study in 22 patients demonstrated 14% weight loss at six months. The pivotal TPS trial randomized 302 patients to TPS or sham device. Weight loss at 12 months was superior with TPS (9.8 vs 2.8%). The few adverse events included esophageal rupture and gastric impaction [239].

Vagal Nerve Blocking Therapy (Vbloc)

With vagal nerve blocking therapy, a pacemaker-like implantable device is surgically placed under the skin, with lead wires placed laparoscopically around the vagus nerve just above the stomach. Activation of the device causes intermittent vagal blockade to induce a sense of satiety. It is FDA approved for weight management in patients with BMI >40 or BMI >35 with weight-related complications [127; 135]. Contraindications include cirrhosis, portal hypertension, hiatal hernia, and other implanted devices (e.g., pacemakers, defibrillators) [127; 135].

In one study, weight loss ≥10% and ≥15% at 12 months (39% and 22%) and 24 months (34% and 21%) was similar among all 123 patients. Adverse events included nausea, reflux, and pain at regulator site. No new adverse effects were noted in the second year of the two-year trial [248]. Weight loss is superior to sham-treated controls but lower than conventional MBS. Despite good safety, the modest efficacy may limit the desirability of intermittent vagal blockade [4].

Liposuction

While not a bariatric procedure, liposuction is a common esthetic procedure that can remove significant amounts of subcutaneous adipose tissue without affecting visceral adipose tissue. In a small 12-week study, women with and without diabetes had 9.1–10.5 kg body fat loss and reduced waist circumference but no improvement in blood pressure, inflammatory markers, or insulin sensitivity [4]. Removal of subcutaneous adipose tissue without reducing ectopic fat depots has little influence on the risk factors related to overweight or obesity [4].

IMPACT ON OBESITY-RELATED CARDIOMETABOLIC ENDPOINTS

MBS effects on major adverse cardiovascular events (a composite of coronary artery events, cerebrovascular events, heart failure, or cardiovascular death), major adverse liver outcomes (progression to cirrhosis, development of hepatocellular carcinoma, liver transplantation, or liver-related death), and obesity-related cancer is of considerable interest [249]. Addressing this are meta-analyses and matched-cohort studies comparing the long-term outcomes of MBS to usual obesity care (controls). Most of these data are retrospective. A noteworthy exception generating many studies is the Swedish Obese Subjects (SOS) project, which has prospectively followed 4,000 bariatric and control patients and a random population reference group of 1,135 over more than 20 years with >98% patient follow-up [250].

In cardiovascular disease outcomes, MBS has been associated with a significantly reduced risk of cardiovascular mortality and incidence of heart failure, myocardial infarction, and stroke [129]. In a 2020 SOS study, patients who had undergone MBS were 30% less likely to die from any cardiovascular disease than controls, including myocardial infarction, heart failure, and stroke, and were 23% less likely to die from cancer. Median life expectancy of MBS patients was 3.0 years longer than controls but 5.5 years shorter than the general population [250].

A 2021 systematic review and meta-analysis found increased median life expectancy of bariatric patients of 9.3 years in those with pretreatment diabetes and 5.1 years among those with no pretreatment diabetes compared with controls. The authors responded to the shorter life expectancy gain from MBS in the 2020 SOS study by citing residual confounding and outdated procedures [251].

In a 2023 SOS study, MBS increased life expectancy by 2.1 and 1.6 years in patients with and without diabetes at a median 26-year follow-up. These authors criticized the 2021 systematic review and meta-analysis for reliance on relatively short-term retrospective data and control patients captured from registers with limited information on health status. MBS benefit in pretreatment type 2 diabetes partly depends on irreversible organ damage (more common with long diabetes duration) and whether short-term or durable remission is achieved (also affected by the severity and duration of diabetes) [252].

Among obese adults with NASH and liver fibrosis, 10-year cumulative incidence of major adverse liver outcomes was 2.3% in those who underwent MBS, compared with 9.6% in controls; major adverse cardiovascular events occurred in 8.5% of MBS participants, compared with 15.7% among controls. For patients with NASH and obesity, MBS was associated with a significantly lower risk of incident major adverse liver outcomes and major adverse cardiovascular events than nonsurgical management [249].

Ten-year outcomes significantly favored MBS in obesity-related cancer incidence (2.9% vs 4.9%) and mortality (0.8% vs 1.4%). Comparable RYGB and sleeve gastrectomy outcomes suggest the primary mechanism is weight loss itself, not procedure-specific physiological alteration. Among MBS patients, cancer incidence was highest in those with weight loss less than 24%. Dose-dependent reduction in cancer risk required substantial weight loss, and the separation of survival curves only appeared six years after the index date [130].

POSTBARIATRIC INTERVENTIONS

Greater comprehension of obesity as a chronic disease requiring long-term management has highlighted the importance of intervention in patients with primary or secondary MBS nonresponse [214]. Nonresponse has been defined as <50% excess weight loss over one to two years following intervention, and weight recurrence is defined as regaining ≥20% of nadir weight loss after MBS [224; 253]. Weight recurrence refers to secondary nonresponse [214]. Estimated rates of nonresponse (11% to 22%) and weight recurrence (16% to 37%) vary by definition used [224; 254].

Causes of weight recurrence include increased caloric intake due to increased appetite and maladaptive or dysregulated eating, inadequate physical activity, and psychosocial stresses. Weight recurrence can promote recurrence of previously controlled type 2 diabetes and other obesity-related complications, with diminished quality of life and poor emotional health. Preventing weight recurrence is a primary goal [224].

Surprisingly, nutritional, cognitive-behavioral, supportive, and other psychological and lifestyle interventions, started perioperatively or up to two years postoperatively, have not demonstrated a significant effect on overall weight loss. Systematic reviews and meta-analyses of these interventions have concluded their efficacy in preventing or reversing weight recurrence is marginal or null [224].

Intervention for patients experiencing nonresponse or weight recurrence entails revisional surgery or adjuvant antiobesity medication [126]. Because most revisional procedures carry higher morbidity than primary procedures, nonsurgical interventions should be tried first [224; 255].

Antiobesity Medication

Antiobesity medications may work synergistically with MBS, and treating patients with obesity via a multimodal approach has the potential to increase and possibly enhance MBS efficacy and durability. The ASMBS supports preoperative use of antiobesity medications for reducing perioperative risk and increasing postsurgery attainment of weight-loss goals and comorbidity resolution as well as post-MBS for ameliorating weight recurrence [124].

Phentermine is one of the most commonly used antiobesity medications in MBS patients. Pairing phentermine with topiramate may be advantageous in weight-loss efficacy through combinatory mechanisms and cost considerations in post-MBS patients. GLP-1 agonists offer high efficacy, few drug interactions, and few side effects, but cost can be a deterrent [124].

In most patients, MBS results in supraphysiological levels of circulating GLP-1. However, patients with poor postsurgery weight loss demonstrate an unfavorable postoperative gut hormone profile, including lower circulating GLP-1 levels. As such, GLP-1 analogs may benefit these patients [256].

In the BARI-OPTIMISE randomized placebo-controlled trial, patients with poor weight loss (≤20%) and suboptimal nutrient-stimulated GLP-1 response one or more years following sleeve gastrectomy or RYGB received liraglutide 3.0 mg or placebo. After 26 weeks, mean total weight loss with liraglutide was 8.82%, compared with 0.54% with placebo [256].

Patients receiving liraglutide for late weight recurrence after RYGB were prospectively followed. After 24 months, patients lost >85% of weight recurrence from nadir; hypertension and dyslipidemia also improved [257].

Weight recurrence studies of GLP-1 RAs have largely used liraglutide. However, semaglutide may be superior to liraglutide for weight recurrence, regardless of MBS procedure. In one study, semaglutide was superior on with 12-month weight loss (13% vs 9%) and odds ratio for ≥15% weight loss (2.55) compared with liraglutide [258].

Patients treated with liraglutide or semaglutide for weight recurrence after RYGB lost 67.4% of the weight regain after six months. More patients on semaglutide had total weight loss ≥10% (47.6% vs 31%) and ≥15% (24% vs 3.5%) [254].

The optimal time to initiate antiobesity medication may be at weight plateau, rather than after weight recurrence [259]. Proactive liraglutide may significantly augment ESG efficacy. Initiated five months after ESG and assessed seven months later, liraglutide/ESG showed greater reductions in weight (25% vs 20.5%) and body fat (10.5% vs 8%) compared with ESG alone at one year postprocedure [260].

Revisions/Conversions

The choice of conversion depends on the type of primary operation and the indication for conversion [125]. Patients may require reoperation (to correct/adjust) or conversion following any primary MBS, but some evidence suggests that more "restrictive" procedures (e.g., LAGB, sleeve gastrectomy) lead to higher rates of reoperation or conversion.

Conversions are the third most common MBS procedure. Of 57,683 performed between 2015 and 2017, most involved gastric band (LAGB) conversion to sleeve gastrectomy (15,433), to RYGB (10,485), or removal (14,715). It is projected that sleeve gastrectomy to RYGB conversions (8,491) will likely surpass LAGB conversions with time [261].

Weight recurrence within several years of sleeve gastrectomy is described as an emerging problem. After seven years, 28% to 30% of patients had weight recurrence and 20% had revisions, mostly due to weight recurrence (13%) and GERD (3%) [262; 263]. However, over 5 to 12 years after RYGB, up to 25% of patients experience <20% weight loss due to nonresponse/weight recurrence [256].

The ASMBS has made several suggestions concerning revisions/conversions, stating that in addition to improving weight loss, type 2 diabetes improvement and remission rates also increase [125]. It is important to consider behavioral factors, such as binge-eating, may be responsible for poor weight outcomes after LAGB reoperation. If necessary, conversions to RYGB or sleeve gastrectomy after LAGB can be performed in one or two stages. If conversion is required due to GERD, the preferred procedure is RYGB. Conversion of sleeve gastrectomy for additional weight loss can be RYGB or duodenal switch, which results in greater weight loss than RYGB but higher risk of long-term nutritional deficiencies [125].

For weight recurrence after sleeve gastrectomy, SADI-S led to greater total weight loss (30% vs 19%) and remission of type 2 diabetes and hypertension, fewer complications and reoperations after five years when compared with OAGB [264]. In one trial, OAGB for 1,075 patients with weight recurrence after various MBS led to two- and five-year excess weight loss of 68.5% and 71.6%, respectively. Adverse events included leak (1.5%), marginal ulcer (2.4%), anemia (2%), and mortality (0.3%) [265].

CONCLUSION

During 1980–2000, obesity prevalence increased roughly 100% as adults consumed less fat and sugar, became more active, and initiated more frequent weight loss attempts with diet and exercise. The obesity epidemic is unexplained by worsening diet and physical inactivity.

Today, it is acknowledged that obesity is a chronic, relapsing disease with cardiometabolic complications (e.g., insulin resistance, hypertension, type 2 diabetes, NAFLD, cardiovascular diseases) arising from adipose mass due to shared pathophysiology. The goal of obesity treatment—long-term weight loss sufficient to ameliorate cardiometabolic morbidity and premature mortality—usually requires antiobesity medications, bariatric surgery, or both.

Recently approved and emerging antiobesity medications are revolutionizing obesity treatment by achieving long-term weight loss previously unattainable without surgical intervention. Reversing the low utilization of medication and surgical treatment begins with ending the stigmatization of patients with obesity.

APPENDIX: PHYSIOLOGY AND PATHOPHYSIOLOGY

As explored throughout this course, knowledge of the mechanisms underlying obesity and advances in the understanding of how and why adiposity persists are essential in the development of new approaches in the treatment of patients with obesity. Healthcare professionals involved in the care of these patients benefit from a clear understanding of the physiology and pathophysiology involved.

NEUROHORMONAL REGULATION OF ENERGY BALANCE AND BODY WEIGHT

The biological system that regulates energy balance and body weight is dominated by a bidirectional feedback loop between the brain and periphery, sometimes called the gut-brain axis [108]. Peripheral tissue (gut, pancreas, adipose tissue) releases hormones, metabolites, and peptides to communicate information about long-term energy stores and short-term nutrient availability to the brain. Because these molecular messengers provide homeostatic feedback of energy availability and status to the brain, they are called signals (of satiety, hunger, adiposity) [266].

These signals of energy balance reach the hypothalamus via the bloodstream and/or the brainstem via afferent vagal pathways that terminate in the nucleus tractus solitarius (nTS) [103; 267]. Brain circuits respond to this input by adjusting metabolism and behavior to acute and long-term needs and modifying energy intake and expenditure to match energy demands. Over time, this homeostatic regulation of energy balance establishes a metabolic set-point [101; 102].

Peripheral signals can be anorexigenic (appetite-suppressing) or orexigenic (appetite-stimulating) and long- or short-term. Long-term signals of energy balance circulate in proportion to fat mass to inform the brain about long-term energy storage in adipose tissue (i.e., adiposity signals) and are always (leptin) or often (insulin) anorexigenic. Short-term signals of nutrient and meal-derived energy availability (i.e., satiety and hunger signals) are gut-released and include [101; 150; 267]:

- Glucagon-like peptide-1 (GLP-1), peptide YY (PYY), glucose-dependent insulinotropic polypeptide (GIP), cholecystokinin (CCK), and oxyntomodulin (OXM), which are all anorexigenic
- Ghrelin, which is orexigenic and known as the "hunger hormone"

In obesity, this system is dysfunctional and generates and sustains excessive adipose tissue mass. Abnormal interaction between peripheral hormones and brain centers of energy homeostasis is a core feature of obesity pathophysiology [3].

The Hypothalamus

The hypothalamus, as the superordinate regulator of energy homeostasis, receives input via the bloodstream, ascending neurons from the brainstem, and descending neurons from cortical areas. It then coordinates energy balance and other homeostatic systems, integrates reciprocal orexigenic and anorexigenic responses, and governs metabolic adaptation [102; 103; 268].

The arcuate nucleus (ARC) of the hypothalamus is adjacent to the median eminence, a circumventricular organ outside the blood brain barrier, giving ARC neurons direct bloodstream access to detect circulating hormones and metabolites. Arcuate neurons are thus 'first-order' neurons, since circulating peripheral signals act directly on them [101; 102; 269].

First-order ARC neurons project to second-order neurons in the paraventricular (PVH), ventromedial, dorsomedial, and lateral hypothalamus. Second-order hypothalamic neurons project to brainstem circuits and midbrain areas [101; 102; 115; 269]. Brainstem circuits respond rapidly to gut signals to control meal size and termination. Brainstem neurons project to hypothalamic areas and communicate to the gut via parasympathetic signals. Many antiobesity medications work by activating receptors on both hypothalamic and brainstem neurons [102; 115].

The hypothalamic integrative capacity is enhanced by crosstalk with corticolimbic systems that process external sensory information, cognitive and emotional control, and reward-based decision making and mediate emotional, cognitive, and executive aspects of ingestive behavior [8].

A salience network in the frontal cortex, ventral and dorsal striatum, and amygdala, associated with motivation, desire, and craving for palatable high-energy food, is more active in obese than lean subjects. An inhibitory network in the dorsolateral prefrontal cortex is activated in subjects instructed to resist craving. This cognitive control ability is greater in patients with the highest weight loss after bariatric surgery. Connectivity between the salience and inhibitory networks (hedonic control) and the hypothalamus (homeostatic control) differs in lean versus obese subjects. The former homeostatic/hedonic ingestive dichotomy has given way to a more unified and integrative control system [8].

The Arcuate Nucleus and the Melanocortin System

In the ARC, the melanocortin system is a critical and conserved pathway of body weight homeostasis and essential to the regulatory function of the hypothalamus in energy balance and homeostasis. The melanocortin system consists of two distinct, functionally antagonistic neuron populations [150; 268; 270; 271; 272]:

Anorexigenic melanocortin neurons (POMC), which release melanocortin peptides (α- and β-MSH) that bind and stimulate melanocortin receptors (MC3R and MC4R) expressed on second-order neurons. Brain-derived neurotrophic factor, corticotropin-releasing hormone, and thyrotropin-releasing hormone mediate the downstream effects of MC4R activation on suppressing food intake.

Orexigenic agouti-related protein (AgRP) neurons, which antagonize melanocortin neurons and receptors by releasing AgRP, gamma-aminobutyric acid (GABA), and neuropeptide Y (NPY). AgRP antagonizes MC3/4R to prevent the anorexigenic effects of α- and β-MSH binding. GABA directly inhibits POMC neurons in the ARC. NPY is the most potent known short-term orexigenic stimulus.

The brainstem has a smaller number of POMC neurons. AgRP neurons solely exist in ARC and send long-distance projections throughout the hypothalamus and brainstem. AgRP neuron expression is negatively correlated with BMI [273].

POMC and AgRP neurons are tightly linked, exert opposite functions in the reciprocal regulation of downstream MC3/4R neurons, and are themselves reciprocally regulated by circulating hormones and neural inputs [274; 275].

Energy Balance and Melanocortin Activity

POMC and AgRP neurons detect and respond to circulating metabolic and hormone signals of short- and long-term deficit or surplus in energy availability [8]. Circulating hormones (e.g., leptin, insulin, ghrelin, GLP-1) bind to their respective receptors (LepR, InsR, GHSR, GLP-1R) on POMC and AgRP neurons [141]. Energy surplus stimulates POMC neurons. Heightened energy demand activates AgRP neurons [3; 276].

The PVH is a major output nucleus for the ARC and receives afferent inputs from POMC and AgRP neurons [102]. It has the highest number of MC4R-expressing neurons in the CNS [271].

POMC neurons are stimulated by positive energy balance, elevated leptin, and insulin. In contrast, AgRP neurons are inhibited by leptin and insulin deficit and activated by negative energy balance and ghrelin.

POMC and AgRP neuron projections both converge on MC4R neurons in the PVH, which anorexigenic melanocortin peptides activate to suppress food intake and enhance energy expenditure, and orexigenic AgRP neuropeptides inhibit to increase food intake [141; 277]. Also, circulating ghrelin binds its receptor on AgRP neurons, which then release NPY [3].

Negative energy balance and prolonged caloric restriction activate AgRP neurons in part by reducing plasma levels of leptin and insulin that inhibit AgRP neurons. Inactivating this inhibitory input activates AgRP neurons and increases the drive to eat, which promotes positive energy balance and recovery of lost weight [7].

Circulating levels of leptin, insulin, and other hormones serve the hypothalamus with feedback about the availability of energy. When circulating levels of these energy signals decrease during prolonged caloric deficit, increased AgRP neuron excitation recapitulates many behaviors and physiological effects associated with starvation, such as enhanced rewarding properties of food, as well as stimulating food intake [277]. Disruption of this fine-tuned control in the arcuate circuitry leads to dysregulation of energy balance and metabolism [8; 266].

Hypothalamic Regulation of Adiposity and Energy Expenditure

White adipose tissue, the dominant body fat, is comprised of fat cells (adipocytes), stores energy in the form of triglycerides, and can increase fat reserves (lipogenesis) or utilize fat as energy (lipolysis) [278]. Melanocortin signaling regulates lipid metabolism and adiposity via the sympathetic nervous system (SNS) activity; disruption promotes lipid uptake, triglyceride synthesis, and fat accumulation in white adipose tissue [150; 275].

The SNS innervates white adipose tissue, and sympathetic terminals are adjacent to more than 90% of adipocytes. The brain releases norepinephrine from sympathetic terminals, which activate α- and β-adrenergic receptors on adipocytes. This sympathetic outflow is the principal initiator of lipolysis, mediated in part by MC3/4R activity on sympathetic cholinergic neurons [271; 276].

A common frustration for individuals trying to lose weight is the marked compensatory reduction in energy expenditure associated with caloric restriction [277]. AgRP neurons, activated by negative energy balance, shift metabolism toward energy conservation by promoting lipid storage and adipogeneses, elevating carbohydrate fuel use, reducing lipolysis, and thus decreasing energy expenditure in adipose tissue, in part, by suppressing sympathetic outflow to white adipose tissue. NPY release increases food intake and decreases energy expenditure via NPY1R-mediated reduction in downstream sympathetic output to adipose tissue [268]. SNS neurons also produce NPY, which induces vasoconstriction and fat tissue expansion [150].

A key point is that through extensive bidirectional communication, adipose tissue importantly influences energy balance, while CNS and hypothalamus play an essential role in controlling systemic metabolism [279].

Hypothalamic POMC Neurons and Cannabinoids

Cannabis use represents a "wildcard" in appetite mediation by the melanocortin system. By activation of cannabinoid receptor 1 (CB1R), cannabis-induced eating is a hallmark of cannabis use [280].

POMC neurons also produce β-endorphin, an opioid peptide that binds the μ-opioid receptor (MOR). CB1R activation selectively increases β-endorphin, but not α-MSH, release by POMC neurons. Beta-endorphin inhibits AgRP neuron activity, and acute CB1R-induced eating is blocked by naloxone, a MOR antagonist [280].

Thus, cannabis stimulates a switch from α-MSH to β-endorphin release by POMC neurons and subsequently increases appetite and food intake (i.e., "the munchies"). This interesting and paradoxical finding argues against an exclusively anorexigenic role of POMC neurons [266].

Brainstem Circuits

The gut communicates information about food ingestion to the brain via vagal afferent fibers in the NTS. Most of these signals act rapidly to promote meal termination, with less impact on energy expenditure or long-term food intake [150; 281]. The NTS receives and integrates the afferent vagal information and communicates this information to other brain regions it innervates [141; 282].

POMC neurons are also expressed in the NTS, where they project to and receive inputs from brain regions that both overlap and are distinct from connections of arcuate POMC neurons [269]. NTS POMC neurons respond to, among other things, gut-secreted CCK and adipocyte-derived leptin [271].

Some NTS neurons project to the parabrachial nucleus, a central node in this ascending pathway. An anorexigenic circuit implicated in satiety and meal termination arises from calcitonin gene-related peptide (CGRP) neurons in the parabrachial nucleus. Activation of CGRP neurons by gastric distention, CCK, and GLP-1 decreases appetite, while inhibition increases meal size [7; 266].

Arcuate nucleus signaling strongly influences CGRP neuron activity [7; 266; 274]. In the ARC, glutamate-releasing/oxytocin-receptor expressing (Vglut2/OxtR) neurons convey an excitatory, fast-acting satiety mechanism. Projections from these neurons converge with GABAergic AgRP projections on MC4R neurons in PVH, a critical second-order node in the regulation of feeding. In the PVH, MC4R neurons release glutamate and excite downstream CGRP neuron targets in the parabrachial nucleus. Thus, the parabrachial nucleus serves as a third-order node in feeding regulation. In addition, AgRP neurons project to the parabrachial nucleus; activation of AgRP neurons stimulate feeding and delays satiation by inhibiting CGRP [7].

Of note, the substantial complexity inherent in food intake regulation cannot be reduced to a small set of interacting neurocircuits, and much remains to be learned [7].

HORMONE, METABOLIC, AND PEPTIDE SIGNALS OF SATIETY, HUNGER AND ADIPOSITY, BY PERIPHERAL TISSUE ORIGIN		
Hormone	**Receptor Locations in CNS**	**Effects on Energy Balance and Obesity**
Adipocyte origin		
Adiponectin	Hypothalamus	↓ Body weight, plasma lipids
Leptin	ARC	↓ Food intake, body weight
Pancreatic cell origin		
Amylin	ARC, AP, VTA, striatum	↑ Satiety ↓ Gastric emptying, food intake
Glucagon (GCG)	ARC, NTS	↑ Satiety, glycogenolysis, gluconeogenesis
Insulin	ARC	↓ Food intake, body weight
Pancreatic polypeptide (PP)	Hypothalamus, NTS	↑ Satiety ↓ Gastric emptying
Enteroendocrine cell origin		
Cholecystokinin (CCK)	Hypothalamus, NTS	↑ Satiety ↓ Gastric emptying/motility
Ghrelin	ARC	↑ Food consumption and reward
GIP	ARC, PVH, DMH	↓ Food intake ↑ LPL, postprandial insulin
Glucagon-like peptide-1 (GLP-1)	ARC, NTS, AP, striatum	↑ Satiety, postprandial insulin ↓ Gastric emptying/motility, food reward
Oxyntomodulin (OXM)	Hypothalamus	↑ Satiety ↓ Gastric emptying, food intake
Peptide tyrosine tyrosine (PYY)	ARC, NTS	↑ Satiety ↓ Gastric emptying/motility
AP = area postrema, ARC = arcuate nucleus of the hypothalamus, CNS = central nervous system, DMH = dorsomedial hypothalamus, GHSR, growth hormone secretagogue receptor, GIP, glucose-dependent insulinotropic polypeptide, NTS = nucleus tractus solitarius, PVH = paraventricular nucleus of the hypothalamus, VTA = ventral tegmental area.		
Source: [115; 147; 267]		*Table 10*

Peripheral Signals of Energy Status

What effect does ghrelin have on energy balance and obesity?

As will be discussed later in this course, many novel and emerging antiobesity medications act through the hypothalamic receptors of peripherally released hormones and peptides. ***Table 10*** summarizes the effects of endogenous and pharmacological ligand-binding of these receptors.

Adipose Tissue and Pancreatic Hormones

Some peripheral signals of energy balance are released by adipocytes (leptin, adiponectin), and pancreatic α cells (GCG), β cells (insulin, amylin), and F cells (pancreatic polypeptide) [150; 282].

Leptin, the canonical signal of adipose tissue mass, is produced by white adipose tissue in approximate proportion to triglyceride stores. Adequate leptin action via its receptor (LepR) on arcuate neurons indicates sufficient energy stores; reduced leptin signaling indicates an energy deficit, promoting hunger and increasing energy intake [281]. LepR activation also decreases body weight by increasing lipolysis and energy expenditure [277]. CCK potentiates leptin effects to decrease food intake and body weight [267].

Normal body-weight maintenance requires intact leptin-regulated neurocircuits. An association of obesity with leptin resistance has been suggested, but some obese individuals may simply require more leptin to fully engage relevant neurocircuits. The primary role of leptin-responsive neurocircuits may relate more to preventing loss of body fat (by decreased leptin signaling to CNS) than defending against its increase (by increased leptin levels) [7].

Adiponectin is an adipocyte-derived protein that decreases body weight and plasma lipid levels and enhances insulin suppression of hepatic glucose production. Adiponectin levels increase following weight loss interventions in obesity, and patients with obesity show an inverse correlation between plasma adiponectin and insulin resistance [115].

Insulin and leptin both circulate in proportion to fat mass. Insulin activates its receptor (IR) expressed in the melanocortin system, which mediates its central anorexigenic effects, decreasing food intake and body weight [115]. Insulin also acts centrally to decrease hepatic glucose output, in part by inhibiting hypothalamic neurons [102]. Insulin inhibits AgRP neuron firing via IR-dependent signaling. Disruption of IR in the CNS promotes obesity with increases in body fat and leptin levels, insulin resistance, elevated insulin levels, and hypertriglyceridemia [266].

Amylin is co-released with insulin from pancreatic β-cells in response to high blood glucose levels, reduces the rate of glucose absorption and inhibits glucagon release. Amylin receptor complexes in the area postrema and brainstem NTS mediate its anorectic effects by activating a central satiety pathway. Amylin also affects hedonic eating by inhibiting reward neurocircuits [141; 267]. Amylin and leptin act synergistically, in part by amylin acting directly on AgRP neurons that co-express LepR. Amylin's ability to slow post-prandial gastric emptying also contributes to satiety [141].

Glucagon (GCG) is secreted by pancreatic α-cells and binds its receptor (GCGR) in the CNS, pancreas, adipocytes, and liver. Glucagon stimulates energy expenditure, reduces food intake, and decreases body weight through multiple mechanisms, including inducing satiety and lipolysis [147; 267]. Hypothalamic GCGR activity inhibits AgRP neuron activity to attenuate orexigenic effects, while central resistance to glucagon-induced hypophagia contributes to the development of obesity [141]. Glucagon's anorectic action seem to be mediated via the liver-vagus-hypothalamus axis [267].

Gut Peptide Hormones

Other signals of energy balance are released by enteroendocrine cells that line the gut, one of the largest hormone-producing organs. Enteroendocrine cells and their respective hormones include L-cells (GLP-1, OXM, PYY), I-cells (CCK), K-cells (GIP), and P/D1 cells (ghrelin). Gut hormones bind their receptors in CNS and on pancreatic β cells (GLP-1, GIP), pancreas (CCK, OXM), and adipocytes (GIP) [147; 267; 283].

Meal termination involves meal-induced enteroendocrine cells release of peptides (e.g., GLP-1, CCK), which promote satiety by activating vagal afferent neurons that relay GI signals to brainstem areas, including the NST [7]. Glucagon-like peptide 1 (GLP-1) increases in circulation following meals and decreases during fasting, stimulates insulin secretion and regulates energy intake, and is also produced in the NTS. GLP-1 acts on GLP-1R in the gut and brain to delay gastric emptying and decrease food intake through activation of satiety pathways and efferent pathways regulating GI function. GLP-1 also reduces glucagon secretion, inhibiting hepatic glucose production [284].

GLP-1 inhibits eating mainly by activating GLP-1R on hypothalamic and brainstem NTS neurons. GLP-1R agonists also suppress hedonic eating by interacting with the mesolimbic reward system, including the ventral tegmental area and nucleus accumbens [267]. GIP and GLP-1 are rapidly degraded by the enzyme dipeptidyl peptidase IV (DPP-IV), leading to a circulating half-life of only two minutes for GLP-1 [150].

GIP acts in concert with GLP-1 on the pancreas after meals to regulate blood glucose by stimulating insulin and glucagon release. GIP contributes to lipid metabolism by promoting lipid storage, adipose tissue blood flow, and triglyceride uptake in adipocytes [284]. The GIP receptor (GIPR) is expressed in arcuate, dorsomedial hypothalamus, and PVH neurons; GIPR activation reduces food intake [267].

Ghrelin circulates as an orexigenic signaler, promoting hunger and meal initiation by binding its receptor (GHSR) on AgRP neurons, which stimulates NPY and AgRP release and inhibits POMC neurons by increasing GABAergic signaling. Vagal afferent neurons also have ghrelin receptors [115; 267]. Compared with lean controls, individuals with obesity have lower circulating ghrelin levels and are more sensitive to its appetite-stimulating effects [115; 267].

Ghrelin and leptin have a reciprocal relationship aimed at increasing or decreasing adiposity. Fasting increases ghrelin and reduces leptin, while high leptin levels suppress gastric ghrelin release and prevent ghrelin-induced NPY neuron activation [141]. Ghrelin and GLP-1 have opposite actions on eating behaviors. Ghrelin reinforces food reward by activating ventral tegmental area dopaminergic neurons; GLP-1 attenuates various palatable food-motivated efforts [267].

Ghrelin remains the only metabolic signal that potently activates orexigenic AgRP neurons. Discovery of an endogenous antagonist of ghrelin, liver-expressed antimicrobial peptide, sparked research interest in it as a possible candidate for obesity treatment [267].

CCK is secreted postprandially and binds CCK1 receptors (CCK1R) expressed in the vagal afferents, brainstem, and hypothalamus to decrease food intake. The satiety signals of CCK are transmitted to the NTS by vagal sensory neurons. CCK activates NTS POMC neurons, and brainstem MC4R signaling is required for CCK-induced appetite suppression [267]. CCK is an acutely acting signal with a very short half-life. Compensatory increases in meal frequency prevent CCK from producing long-term effects on total food intake or body weight [102].

OXM is secreted with GLP-1 and PYY in the postprandial state and exerts its anorectic action primarily via GLP-1R and secondarily via GCGR. The GLP-1R-mediated effects of OXM differ from those of GLP-1. OXM decreases body weight by lowering food intake and increasing energy expenditure and may act via different hypothalamic pathways than those of GLP-1 [267].

PYY is co-secreted with GLP-1 following a meal. Its major circulating form (PYY3-36) binds Y2R expressed on AgRP neurons, inhibiting these neurons and activating POMC neurons. Thus, PYY reduces appetite and body weight by increasing anorexigenic melanocortic activity in the arcuate [267].

PATHOPHYSIOLOGY

Long-term positive energy balance and increased fat mass promote pathogenic adipocyte hypertrophy and adipose tissue accumulation and dysfunction, resulting in immunopathies, endocrinopathies, increased circulating free fatty acids, and lipotoxicity. The OMA uses the term adiposopathy, or "sick fat disease," to describe pathogenic adipose tissue [128].

The consequences of adiposopathy contribute to metabolic diseases including type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, NAFLD, and cancer [18; 29]. Obesity-related metabolic and cardiovascular diseases can be termed cardiometabolic disease or metabolic syndrome.

Adiposopathy is analogous to the disease state of other organs, such as myopathy, cardiomyopathy and encephalopathy. In the disease of adiposopathy, pathogenic enlargement of fat cells and the fat organ results in anatomic and functional abnormalities, metabolic and biomechanical morbidities, and increased mortality [18; 29].

Adipose Cell and Tissue Function

Part of understanding obesity as a disease is recognizing that adipocytes and adipose tissue have vital functions beyond energy storage alone [128]. Adipose tissue is mostly comprised of adipocytes, regulates multiple body processes critical to energy and metabolic homeostasis, and is functionally classified into two types: white and brown [128; 285]. White adipose tissue is an active endocrine and immune organ that includes subcutaneous adipose tissue and visceral (abdominal) adipose tissue and primarily stores energy. However, subcutaneous adipose tissue contains brown-like inducible adipocytes that perform mitochondrial and thermogenic functions and burn fat [286].

Brown adipose tissue, comprising 1% to 2% of body fat, has more mitochondria (thus its brown appearance) and is abundant in neonates but decreases in adults and decreases further in obese adults [286]. Brown adipose tissue produces heat energy, termed thermogenesis, upon β-adrenergic stimulation [287].

Subcutaneous adipose tissue is the largest fat depot. Visceral adipose tissue is more metabolically active, vascular, and innervated than subcutaneous tissue. Ectopic fat, a third depot, is strictly pathogenic [48].

Fat depots are sexually dimorphic; on average, men have more visceral adipose tissue, and women have larger subcutaneous adipose tissue stores. Given the relative impact of fat depots on metabolic health, this sexual dimorphism may explain sex differences in metabolic disease risk until menopause, when decreased estrogen may increase low-density lipoprotein, triglycerides, visceral fat, morbidity, and mortality in women [48].

Adipocytes, which constitute the largest cell volumes in adipose tissue and are the defining fat cell type, have three important roles: lipid storage, insulin sensitivity, and secretory function. Disruption of any contributes to obesity-related metabolic disease states [288].

Some key players in adipose tissue physiology and obesity pathophysiology include glucose, glycogen, triglycerides, and insulin [289; 290]. Glucose is a carbohydrate, one of three macromolecule classes (with fats and proteins); some argue alcohol is a fourth class. Glycogen is the storage form of glucose in liver and muscle. Triglyceride, the storage form of fatty acids, is made of three fatty acids linked to glycerol. The capacity to store carbohydrates (as glycogen) is limited. What cannot be stored as glycogen, or quickly used, gets stored as triglyceride. Insulin, released by pancreatic β-cells in response to rising blood glucose, aims to store carbohydrate as glycogen or fatty acids.

Lipid Storage

During energy surplus, 60% to 80% of excess calories are stored as triglyceride by adipocytes [291]. Adipocytes can increase fat stores (lipogenesis) or release fatty acids (lipolysis) to supply other tissues with energy [278; 285]. Insulin is critically involved in these processes.

For lipogenesis, adipocytes accumulate lipid through free fatty acids from circulating triglyceride and by synthesizing triglyceride from non-lipid metabolite sources, termed de novo lipogenesis [285]. For lipolysis, enzymatic cleavage of triglyceride by lipases generates glycerol and free fatty acids, which are released into circulation for use by organs as fuel (e.g., glycerol for liver gluconeogenesis) [288]. Lipolysis is controlled by sympathetic nervous system input and norepinephrine. In the fasting state, insulin levels drop, releasing norepinephrine, which promotes lipolysis [288].

Because adipose tissue is central to the regulation of systemic lipid metabolism, a balance between lipogenesis and lipolysis within adipocytes is required to maintain insulin sensitivity and energy homeostasis. Nutrient (free fatty acids and glucose) and hormonal cues regulate both processes [288].

Insulin Sensitivity

Insulin sensitivity of adipose tissue is vital to metabolic homeostasis and systemic energy balance [285]. Insulin binds to its receptor in liver, muscle, and adipose tissue to initiate several processes [48; 292].

Insulin activates glucose transporter-4 (GLUT4) on cell surfaces, which transport glucose from the bloodstream into cells. On fat cells, insulin accelerates glucose delivery into adipocytes and induces breakdown of glucose into triglycerides for storage.

Insulin upregulates lipoprotein lipase on fat cell surfaces that bring free fatty acids into adipocytes to store them triglycerides. Insulin also increases triglyceride accumulation by inhibiting their breakdown and release as free fatty acids.

The primary source of glucose for all tissues and largest glucose storage site (as glycogen) is the liver. Hepatocytes are critical intermediaries in energy (lipid, carbohydrate) metabolism. Insulin decreases glucose output by the liver, the main target for pancreatic insulin and glucagon [292; 293].

During caloric deficit, low insulin disinhibits lipolysis, which mobilizes lipids to meet energy demand. However, elevated insulin during caloric excess stimulates glucose uptake, inhibits lipolysis, and orchestrates de novo lipogenesis. The body goes into "storage" mode of carbohydrates and fat. These normal functions of insulin help protect against the cellular and tissue toxicity caused by high circulating glucose and free fatty acids [285; 289].

Endocrine and Immune (Secretory) Function

As an endocrine/immune organ, adipose tissue releases adipokines (via adipocytes) and receives (via receptors) metabolic signals to influence and regulate adipogenesis, lipid metabolism (lipogenesis and lipolysis), appetite and energy balance, inflammatory and immune response, glucose homeostasis (insulin sensitivity), vascular homeostasis (endothelial function), blood pressure, and other processes [128; 285; 288].

Adipokines are hormones, cytokines, extracellular matrix proteins, and growth factors that transmit information from fat tissue to other metabolic organs. They can act locally (paracrine) and/or systemically (endocrine) [128; 285]. Adipocytes express receptors for nuclear and traditional hormones, adipokines, neuropeptides, lipoproteins, prostaglandins, endocannabinoids, and others [128]. Several adipokine hormones, including leptin and adiponectin, are regulators of systemic lipid and glucose homeostasis [285; 288; 294].

Accordingly, adipose tissue can release pro-inflammatory hormones (leptin), cytokines (e.g., tumor necrosis factor-alpha [TNF-a], interleukin-6 [IL-6], IL-8), acute phase response proteins (e.g., C-reactive protein [CRP]), chemokines (e.g., monocyte chemoattractant protein–1 [MCP-1]), and prostaglandins. In addition, adipose tissue can release anti-inflammatory hormones (adiponectin), interleukins (IL-10), and transforming growth factor beta 1 (TGF-beta) [128; 295; 296].

Pathogenesis of Adiposopathy and Obesity-Related Complications

An immune response appears early during adipose accumulation. With excessive fat mass, local adipose-induced inflammatory processes progress to widespread systemic inflammation that damages distant tissue and induces a host of metabolic disorders and organ tissue complications in obesity [194; 297].

Local Pathogenesis

Adipose tissue contains adipocytes, vascular cells, fibroblasts, cells of the innate (e.g., monocytes, macrophages, natural killer cells) and adaptive (e.g., lymphocytes) immune systems, and other cell types essential to its normal physiology that become abnormally altered and interact in the pathophysiology of obesity-related cardiometabolic complications [285; 296]. To expand triglyceride storage as obesity develops and fat mass increases further, adipocytes abnormally increase in number (hyperplasia), then in size (hypertrophy) [278; 285]. Hypertrophy compromises the function of adipose tissue, degrading the extracellular matrix which promotes a switch toward fibrosis that restricts adipocyte fat storage [295; 298].

Triglyceride accumulation promotes hypoxia, apoptosis, and oxidative and mitochondrial stress in adipocytes and release of pro-inflammatory factors [287; 296]. As obesity advances, lipid-laden hypertrophied adipocytes undergo necrotic and/or apoptotic cell death, contributing to the recruitment of inflammatory cells and to adipose tissue dysfunction [298].

Adipose tissue macrophages are essential for maintaining adipose tissue energy homeostasis and inflammatory response [291]. The adipose tissue macrophage phenotypic correlates to BMI and adipocyte size [296]. The obesity-induced M1 phenotype is associated with inflammation and tissue destruction; M1 may comprise 50% of all adipose tissue cells (compared with 10% to 15% in lean adults) [298; 299].

As adipose tissue expands, angiogenesis lags. The hypoxic state triggers an inflammatory response, which initiates monocyte recruitment and differentiation into M1 adipose tissue macrophages [299]. Circulating macrophages infiltrate adipose tissue, producing MCP-1, which recruits more inflammatory cells to adipose tissue and TNF-a and further promotes MCP-1 production by adipocytes, recruiting yet more immune cells to adipose tissue. The M2 to M1 shift aggravates a vicious cycle of chronic low-grade inflammation [128; 285].

Systemic Pathogenesis

The inflammatory adipose tissue microenvironment diffuses systemically and to remote organ sites. MCP-1 recruitment and proliferation into liver, adipose, pancreatic islet, intestine, and muscle tissue induces a pro-inflammatory M1 state [299]. Cytokines (TNF-a, IL-1b, IL-6) and adipokines (leptin) activate systemic and organ-specific inflammatory signaling pathways, impairing β-cell function, suppressing insulin secretion, and promoting accumulation of ectopic fat, insulin resistance and hyperglycemia [287; 297; 298; 300].

Adiposopathic tissue pumps free fatty acids into circulation, leading to ectopic pathogenic deposition of fatty acids into pericardial and perivascular fat depots, within/around the liver, muscle, heart, pancreas, and kidney [128]. Ectopic fat intensifies local inflammatory activity and promotes lipotoxicity [300].

Insulin resistance in adipocytes impedes fat storage, accelerates lipolysis and further increases plasma free fatty acids, promoting insulin resistance in liver and muscle, hepatic steatosis and dyslipidemia, and contributing to β-cell failure. Insulin resistance in muscle and fat is marked by impaired glucose transport from circulation due to M1 inhibition of GLUT4, leading to hyperglycemia [301].

Increased ectopic fat deposition, lipotoxicity from excess circulating free fatty acids, glucose toxicity, along with β-cell resistance to GLP-1, cause progressive failure of β-cell functioning. Increased glucagon and enhanced liver sensitivity to glucagon lead to excessive hepatic glucose production. Increased renal glucose reabsorption by sodium/glucose co-transporter 2 (SGLT2) helps maintain hyperglycemia.

Insulin resistance in obesity leads to chronic compensatory hyperinsulinemia, which in turn promotes further weight gain [302]. This is exacerbated by resistance to the anorexigenic effects of insulin, leptin, GLP-1, amylin, and PYY [303].

Insulin resistance, hyperglycemia, and hyperinsulinemia in obesity promote hypertension, dyslipidemia, endothelial dysfunction, and a prothrombotic state, leading to NAFLD and type 2 diabetes [304]. NAFLD increases the risk of liver cirrhosis and hepatocellular carcinoma and is strongly correlated with cardiovascular disease and type 2 diabetes [305].

Type 2 diabetes, the predominant consequence of insulin resistance accounting for more than 90% of all diabetes cases, can lead to disabling and life-threatening microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (cardiovascular disease) complications [304; 306].

Biomechanical Consequences of Obesity

Local biomechanical stress due to excessive fat mass and body weight (e.g., on the joints, respiratory tract, blood vessels or within the abdominal compartment) causes and/or exacerbates morbidities common in patients with obesity, such as knee osteoarthritis, back pain, restrictive lung disease, obstructive sleep apnea, gastroesophageal reflux disease (GERD), hernias, and chronic venous insufficiency. These complications are further aggravated by the adverse metabolic profile and chronic inflammatory state in obesity, amplifying the overall burden of the disease and creating a vicious cycle that can be effectively broken only by sustained weight loss [302].

"Metabolically Healthy" Obesity

The concept of metabolically healthy obesity has been described in the literature. In general, it is defined as obesity in the absence of type 2 diabetes, hypertension, and hypercholesterolemia. Some have questioned the cardiovascular disease risk of persons with metabolically healthy obesity, suggesting this as a low-risk phenotype [307]. However, a large cohort demonstrated that obesity is a risk factor for cardiovascular disease regardless of whether the individual remained metabolically healthy over long periods [308]. Furthermore, a study of 270 patients who met strict inclusion criteria for metabolically healthy obesity found that even with strict criteria to eliminate all patients with any metabolic problems, a significant proportion had unsuspected NAFLD (35.5%); some had steatohepatitis (8.2%) and liver fibrosis (4.4%) [305].

Psychiatric Disorders

The neuropathological processes that lead to psychiatric disorders share common brain pathways with those that lead to obesity, metabolic syndrome, and cardiovascular disease risk factors, each of which can influence the risk for the others. Evidence points to a critical role for two major pathways: inflammatory processes that induce alterations of brain functions, and chronic stimulation of the hypothalamic-pituitary-adrenal (HPA) axis [87].

Psychiatric disorders are often characterized by a chronic HPA axis activation and sustained cortisol elevation, both of which are linked to abdominal obesity, hepatic steatosis, insulin resistance, and cardiovascular disease. Conversely, increased adiposity leads to chronic low-grade activation of inflammatory processes, which plays a potent role in the pathophysiological brain alterations associated with psychiatric disease. Thus, adiposity-driven inflammation may contribute to the growing prevalence of mood disorders [87].

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

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#30613 • 15 ANCC / 6 Advanced 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

TREATMENT OF HEART FAILURE: AN UPDATE
#30934 • 10 ANCC / 3 Advanced Pharm Hours
Book By Mail – $68 • ONLINE – $60
Purpose: The purpose of this course is to provide nurses and ancillary nursing personnel with current information about the scientific advances in the treatment of acute heart failure.
Faculty: Patricia Lea, RN, DNP, MSEd, CCRN
Audience: This course is designed for nurses and ancillary nurse personnel involved in the treatment and continued assessment of patients with heart failure.
Additional Approval: AACN Synergy CERP Category A, CCMC

SHARPS SAFETY AND NEEDLESTICK PREVENTION
#31022 • 2 ANCC Hours
Book By Mail – $23 • ONLINE – $15
Purpose: The purpose of this course is to encourage awareness of all types of sharps exposures and improve adherence to injury-prevention strategies.
Faculty: Carol Shenold, RN, ICP
Audience: This course is designed for nurses in all practice settings.
Additional Approval: AACN Synergy CERP Category A

COMMUNICATION AND SOFT SKILLS IN NURSING PRACTICE
NEW!
#31350 • 3 ANCC Hours
Book By Mail – $26 • ONLINE – $18
Purpose: The purpose of this course is to provide nurses with strategies to support the soft skills needed to provide optimal patient care and enhance professionalism in health care.
Faculty: Mary Franks, MSN, APRN, FNP-C
Audience: This course is designed for nurses in all practice settings.
Additional Approval: AACN Synergy CERP Category C

CHILDHOOD OBESITY: IMPACT ON HEALTH CARE
UPDATE
#32014 • 5 ANCC / 1 Advanced Pharm Hour
Book By Mail – $38 • ONLINE – $30
Purpose: The impact of childhood obesity on an already stressed healthcare system is high and is estimated to rise as the diagnoses of comorbid conditions continue to occur at a younger age. The purpose of this course is to provide nurses with the information necessary to improve the care of children and adolescents who are overweight or obese.
Faculty: Diane Thompson, RN, MSN, CDE, CLNC
Audience: This course is designed for nurses in all practice settings with a desire to better understand the issues facing obese children and their families and the impact of childhood obesity on national and global health care.
Additional Approval: AACN Synergy CERP Category A, CCMC

DIABETIC HYPOGLYCEMIA
#34654 • 5 ANCC / 5 Advanced Pharm Hours
Book By Mail – $38 • ONLINE – $30
Purpose: The purpose of this course is to provide nurses and healthcare professionals with a foundation of understanding hypoglycemia in order to assure the highest quality of care is provided to patients.
Faculty: Diane Thompson, RN, MSN, CDE, CLNC
Audience: This course is designed for nurses in any healthcare venue and dietitians with a desire to better understand the causes, recognition, and treatment of hypoglycemia in a variety of settings.
Additional Approval: AACN Synergy CERP Category A, CCMC

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Course Availability List *(Cont'd)*

ETHICAL DECISION MAKING
#37074 • 15 ANCC Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to assist healthcare professionals to define the predominant ethical theories and principles used in health care, determine any legal and regulatory implications, and in collaboration with their colleagues and patients/clients, make effective decisions that determine the appropriate course of treatment, or refusal of such, for and with those for whom they care.
Faculty: Michele Nichols, RN, BSN, MA
Audience: This course is designed for all nurses and allied healthcare professionals.
Additional Approval: AACN Synergy CERP Category B, CCMC

PULMONARY EMBOLISM
#90120 • 2 ANCC /
1 Advanced Pharm Hour

NEW!

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to provide healthcare professionals with the knowledge and clinical strategies necessary to optimally triage and treatment patients with pulmonary embolism.
Faculty: Dalia Saha, MD
Audience: This course is designed for physicians, PAs, and nurses involved in assessing, triaging, and managing patients with suspected pulmonary embolism.
Additional Approval: AACN Synergy CERP Category A

HIPAA PRIVACY AND SECURITY
#91140 • 5 ANCC Hours

NEW!

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide information that will allow health and mental health professionals to more easily comply with the Privacy and Security Rules defined by HIPAA.
Faculty: Carol Shenold, RN, ICP
Audience: This course is designed for all members of the interprofessional healthcare team.
Additional Approval: AACN Synergy CERP Category B, CCMC

MATERNAL HEALTH DISPARITIES
#93010 • 4 ANCC Hours

NEW!

Book By Mail – $32 • ONLINE – $24

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

PREDIABETES: AN OPPORTUNITY TO PREVENT DIABETES
#94194 • 15 ANCC /
7 Advanced Pharm Hours

UPDATE

Book By Mail – $98 • ONLINE – $90

Purpose: Studies have shown that diabetes can be delayed or prevented in people with prediabetes, but risk reduction relies heavily on lifestyle changes on the part of the patients, making education and counseling of vital importance. The purpose of this course is to provide healthcare professionals with the information and skills necessary to effectively deal with this common condition and learn ways to help patients make healthy lifestyle choices.
Faculty: Susan Semb, MSN, CDCES
Audience: This course is designed for nurses in adult primary care, clinical, and acute care settings, healthcare and behavioral health professionals in public health and preventive medicine settings, and health education specialists.
Additional Approval: AACN Synergy CERP Category A

ELDER ABUSE: CULTURAL CONTEXTS AND IMPLICATIONS
#97824 • 5 ANCC Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to increase the knowledge base of nurses, physicians, and other allied health professionals about elder abuse, assessment, and intervention. This curriculum will focus on abuse against elders in domestic settings perpetrated by family members.
Faculty: Alice Yick Flanagan, PhD, MSW
Audience: This course is targeted to physicians, nurses, and other allied health professionals who may identify and intervene in cases of elder abuse.
Additional Approval: AACN Synergy CERP Category B, CCMC

CANNABINOID OVERVIEW
#98010 • 3 ANCC /
3 Advanced Pharm Hours

NEW!

Book By Mail – $26 • ONLINE – $18

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the various cannabinoids.
Faculty: Chelsey McIntyre, PharmD
Audience: This course is designed for healthcare professionals whose patients are taking or are interested in taking cannabinoid products.
Additional Approval: AACN Synergy CERP Category A

Prices are subject to change.
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Course Availability List *(Cont'd)*

COMMONLY ABUSED SUPPLEMENTS

#98020 • 2 ANCC Hours

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the commonly abused supplements and their adverse effects.
Faculty: Chelsey McIntyre, PharmD
Audience: This course is designed for healthcare professionals whose patients are taking or are interested in taking dietary supplements.
Additional Approval: AACN Synergy CERP Category A

GETTING TO THE POINT: ACUPUNCTURE AND ACUPOINT THERAPIES

#98030 • 4 ANCC Hours

Book By Mail – $32 • ONLINE – $24

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of acupoint and acupressure therapies.
Faculty: Chelsey McIntyre, PharmD
Audience: This course is designed for healthcare professionals whose patients are using or are interested in using acupoint and acupressure therapies.
Additional Approval: AACN Synergy CERP Category A

PARKINSON DISEASE

#98772 • 10 ANCC / 5 Advanced Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide physicians, nurses, and other members of the interprofessional healthcare team a review of pathogenesis, disease progression, diagnosis, and management of Parkinson disease, in order to improve patient care and quality of life.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for all healthcare providers in the primary care setting who may encounter patients with Parkinson disease.
Additional Approval: AACN Synergy CERP Category A, CCMC

FOOD ALLERGIES

#98793 • 5 ANCC / 2 Advanced Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to encourage healthcare professionals in the primary care setting to raise the issue of reactions to food during patient encounters, especially with parents of young patients, and to educate patients about the importance of protecting themselves or their children from allergic reactions.
Faculty: Lori L. Alexander, MTPW, ELS, MWC
Audience: This course is designed for pediatricians, other physicians, physician assistants, nurses, nurse practitioners, and members of the interdisciplinary team involved in the care of patients with food allergies who would benefit from a better understanding of the natural history, diagnosis, and treatment of food allergies.
Additional Approval: AACN Synergy CERP Category A

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

#98813 • 10 ANCC / 8 Advanced Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide healthcare professionals a current review of pathogenesis, diagnosis, assessment, and treatment of chronic obstructive pulmonary disease (COPD), emphasizing strategies for prevention and best practice clinical guidelines for managing the stable patient and COPD exacerbations.
Faculty: John M. Leonard, MD
Audience: This course is designed for physicians, primary care providers, nurses, respiratory therapists, and medical assistants involved in the care of patients with COPD.
Additional Approval: AACN Synergy CERP Category A, CCMC

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4. Did the course content support the stated course objective?
5. Did the course content demonstrate the author's knowledge of the subject?
6. Was the course content free of bias?
7. Before completing the course, did you identify the necessity for education on the topic to improve your nursing practice?
8. Have you achieved all of the stated learning objectives of this course?
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10. Did study questions throughout the course promote recall of learning objectives?
11. Did evidence-based practice recommendations assist in determining the validity or relevance of the information?
12. Are you more confident in your ability to provide nursing care after completing this course?
13. Do you plan to make changes in your nursing practice as a result of this course content?

#31374 Ohio Nurse Practice Act 1 Contact Hour	**#97770** Counseling Patients at the EOL 5 Contact Hours	**#34344** Pressure Injuries & Skin Care 5 Contact Hours	**#94280** Obesity Management 15 Contact Hours
1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review
2. _____ Hours	2. _____ Hours	2. _____ Hours	2. _____ Hours
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4. ☐ Yes ☐ No	4. ☐ Yes ☐ No	4. ☐ Yes ☐ No	4. ☐ Yes ☐ No
5. ☐ Yes ☐ No	5. ☐ Yes ☐ No	5. ☐ Yes ☐ No	5. ☐ Yes ☐ No
6. ☐ Yes ☐ No	6. ☐ Yes ☐ No	6. ☐ Yes ☐ No	6. ☐ Yes ☐ No
7. ☐ Yes ☐ No	7. ☐ Yes ☐ No	7. ☐ Yes ☐ No	7. ☐ Yes ☐ No
8. ☐ Yes ☐ No	8. ☐ Yes ☐ No	8. ☐ Yes ☐ No	8. ☐ Yes ☐ No
9. ☐ Yes ☐ No	9. ☐ Yes ☐ No	9. ☐ Yes ☐ No	9. ☐ Yes ☐ No
10. ☐ Yes ☐ No	10. ☐ Yes ☐ No	10. ☐ Yes ☐ No	10. ☐ Yes ☐ No
11. ☒ N/A	11. ☐ Yes ☐ No	11. ☐ Yes ☐ No	11. ☐ Yes ☐ No
12. ☐ Yes ☐ No	12. ☐ Yes ☐ No	12. ☐ Yes ☐ No	12. ☐ Yes ☐ No
13. ☐ Yes ☐ No	13. ☐ Yes ☐ No	13. ☐ Yes ☐ No	13. ☐ Yes ☐ No

#31374 The Ohio Nurse Practice Act — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

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