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FOR PENNSYLVANIA PHYSICIANS
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Child Abuse Identification and Reporting: The Pennsylvania Requirement

This course is approved by the Pennsylvania Department of Human Services to fulfill the requirement for 2 hours of Child Abuse Recognition and Reporting (Act 31) training for healthcare professionals renewing their license. Provider number CACE000020.

We report your credit within 24 hours of processing your order.

In addition to receiving *AMA PRA Category 1 Credit™*, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board: 3 ABIM MOC Points, 3 ABS Points, 3 ABP MOC Points, 3 ABA MOC Points, 3 ABPath Points.

Audience
This course is designed for all Pennsylvania physicians, physician assistants, nurses, social workers, counselors, pharmacists, and allied health professionals required to complete child abuse education.

Course Objective
The purpose of this course is to enable healthcare professionals in all practice settings to define child abuse and identify the children who are affected by violence. This course describes how a victim can be accurately diagnosed and identifies the community resources available in the state of Pennsylvania for child abuse victims.

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

1. Summarize the historical context of child abuse.
2. Discuss the emergence of the child welfare system in Pennsylvania.
3. Define child abuse and neglect and identify the different forms of child abuse and neglect.
4. Discuss the scope of child abuse and neglect in the United States and specifically in Pennsylvania.
5. Review the mandatory reporting process and mandated reporters in the state of Pennsylvania, including possible barriers to reporting suspected cases of child abuse.

Faculty
Alice Yick Flanagan, PhD, MSW, received her Master's in Social Work from Columbia University, School of Social Work. She has clinical experience in mental health in correctional settings, psychiatric hospitals, and community health centers. In 1997, she received her PhD from UCLA, School of Public Policy and Social Research. Dr. Yick Flanagan completed a year-long post-doctoral fellowship at Hunter College,

School of Social Work in 1999. In that year she taught the course Research Methods and Violence Against Women to Masters degree students, as well as conducting qualitative research studies on death and dying in Chinese American families. (A complete biography can be found online at www.NetCE.com.)

Faculty Disclosure
Contributing faculty, Alice Yick Flanagan, PhD, MSW, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner
John M. Leonard, MD

Senior Director of Development and Academic Affairs
Sarah Campbell

Division Planner/Director Disclosure
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This activity has been approved for the American Board of Anesthesiology's® (ABA) requirements for Part II: Lifelong Learning and Self-Assessment of the American Board of Anesthesiology's (ABA) redesigned Maintenance of Certification in Anesthesiology Program® (MOCA®), known as MOCA 2.0®. Please consult the ABA website, www.theABA.org, for a list of all MOCA 2.0 requirements. Maintenance of Certification in Anesthesiology Program® and MOCA® are registered certification marks of the American Board of Anesthesiology®. MOCA 2.0® is a trademark of the American Board of Anesthesiology®.

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 3 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

This activity has been designated for 3 Lifelong Learning (Part II) credits for the American Board of Pathology Continuing Certification Program.

Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

Special Approvals
This course is approved by the Pennsylvania Department of Human Services to fulfill the requirement for 3 hours of Child Abuse Recognition and Reporting (Act 31) training for healthcare professionals applying for licensure. Provider number CACE000020.

This course is approved by the Pennsylvania Department of Human Services to fulfill the requirement for 2 hours of Child Abuse Recognition and Reporting (Act 31) training for healthcare professionals renewing their license. Provider number CACE000020.

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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HISTORICAL CONTEXT

Today, there is an established system in the United States to respond to reports of child abuse and neglect; however, this has not always been the case. This is not because child abuse, neglect, and maltreatment are new social phenomena. Rather, the terms "child abuse," "child neglect," and "child maltreatment" are relatively new, despite the fact that this social problem has existed for thousands of years [1]. Cruelty to children by adults has been documented throughout history and across cultures. In China, infant girls were often neglected during times of famine or sold during times of extreme poverty. There is also historical evidence that cultures have taken steps to stop child abuse and cruelty. For example, 6,000 years ago in Mesopotamia, orphans had their own patron goddesses for help and protection [2].

In many cases, the physical abuse of children has been linked to punishment. Throughout history, physical child abuse was justified because it was believed that severe physical punishment was necessary to discipline, rid the child of evil, or educate [2; 13]. It was not until 1861 that there was a public outcry in the United States against extreme corporal punishment. This reform was instigated by Samuel Halliday, who reported the occurrence of many child beatings by parents in New York City [2].

Sexual abuse of children, particularly incest (defined as sex between family members), is very much a taboo. The first concerted efforts to protect children from sexual abuse occurred in England during the 16th century. During this period, boys were protected from forced sodomy and girls younger than 10 years of age from forcible rape [2]. However, in the 1920s, sexual abuse of children was described solely as an assault committed by "strangers," and the victim of such abuse was perceived as a "temptress" rather than an innocent child [2].

The first public case of child abuse in the United States that garnered widespread interest took place in 1866 in New York City. Mary Ellen Wilson was an illegitimate child, 10 years of age, who lived with her foster parents [3]. Neighbors were concerned that she was being mistreated; however, her foster parents refused to change their behaviors and said that they could treat the child as they wished [2]. Because there were no agencies established to protect children specifically, Henry Berge, founder of the Society for the Prevention of Cruelty to Animals, intervened on Mary's behalf [3]. He argued that she was a member of the animal kingdom and deserved protection. The case received much publicity, and as a result, in 1874 the New York Society for the Prevention of Cruelty to Children was formed [3]. Because of this case, every state now has a system in place for reporting child abuse. The Pennsylvania Department of Public Welfare (now known as the Department for Human Services) was established in 1921 and part of its original intent was to care for "dependent, defective, and delinquent children" [7].

As a result of Berge's advocacy for children's safety, other nongovernmental agencies were formed throughout the United States, and the establishment of the juvenile court was a direct result of the Society for the Prevention of Cruelty to Children [13]. By 1919, all but three states had juvenile courts. However, many of these nongovernmental agencies could not sustain themselves during the Depression [13].

The topic of child abuse and neglect received renewed interest in the 1960s, when a famous study titled "The Battered-Child Syndrome" was published [1; 4]. In the study, researchers argued that the battered-child syndrome consisted of traumatic injuries to the head and long bones, most commonly to children younger than 3 years of age, inflicted by parents [1; 4]. The study was viewed as the seminal work on child abuse, alerting both the general public and the academic community to the problems of child abuse [1; 2]. Soon, all 50

states required physicians to report child abuse [14]. In the early 1970s, Senator Walter Mondale noted that there was no official agency that spent its energies on preventing and treating child maltreatment [13]. Congress passed the Child Abuse Prevention and Treatment Act (CAPTA) of 1974, which targeted federal funds to improve states' interventions for the identification and reporting of abuse [13]. In 2010, additional prevention and treatment programs were funded through CAPTA, and in 2012, the Administration on Children, Youth, and Families began to focus on protective factors to child abuse and neglect [61].

Today, child abuse and neglect are considered significant social problems with deleterious consequences. As noted, a system has been implemented in all 50 states to ensure the safety of children, with laws defining what constitutes abuse and neglect and who is mandated to report.

CHILD WELFARE IN PENNSYLVANIA

The Children's Aid Society of Pennsylvania, one of the first organizations to advocate for children and their welfare in the United States, was founded in 1882 [62]. In the following years, the Children's Aid Society was instrumental in educating the public about the unsanitary and unsafe conditions in almshouses, which were sometimes used for orphaned or abandoned children. Subsequently, legislation was passed in Pennsylvania to ensure that children were not permanently placed in almshouses [62].

In the state of Pennsylvania, Act 91 was passed in 1967 and gave child welfare agencies in all counties the responsibility to investigate child abuse reports made by physicians [18]. Three years later, Act 91 was modified to include school nurses and teachers as mandated reporters [18].

Pennsylvania was also the first state to take a noncriminal view of child abuse [22; 26]. In 1975, the Child Protective Services Law was enacted, which established a child abuse hotline and a statewide central registry in Pennsylvania in order to encourage the reporting of child abuse [18; 26].

The child welfare system in Pennsylvania is supervised by the state but administered by the different local counties [27]. This means that there are a total of 67 county agencies that administer the child welfare and juvenile justice services [27]. Aside from frank abuse, reports of other acts that might affect the well-being of a child are also accepted. The State of Pennsylvania delineates two functions for the local agencies: child protective services (CPS) and general protective services (GPS).

In 2016, SB1311 (Act 115) was signed and went into effect. This Act provides for additional grounds for involuntary termination of parental rights, provides for an additional grounds for aggravated circumstances, allows for the release of information in confidential reports to law enforcement when investigating cases of severe forms of trafficking in persons of sex trafficking, and adds a category of child abuse to include human trafficking. In 2017, Governor Tom Wolf approved Act 68 (also known as the Newborn Protection Act) to increase the number of locations for parents to give up their newborn without criminal liability [63]. In 2018, Act 29 was signed and expanded the definition of child abuse in Pennsylvania to include leaving a child unsupervised with a sexual predator [64]. That same year, Act 54 was signed and required mandatory notification when a medical provider has determined that a child (younger than 1 year of age) was born affected by substance use or withdrawal symptoms resulting from prenatal drug or alcohol exposure. This Act also mandates the development of "interagency protocols" to support local multidisciplinary teams to identify, assess, and develop a plan of safe care for infants born affected by substance use or withdrawal symptoms. In 2019, Act 88, relating to penalties for failure to report or refer, was enacted.

CHILD PROTECTIVE SERVICES

CPS is in place to address acts that are "non-accidental serious physical or mental injury, sexual abuse, or exploitation, or serious physical neglect caused by acts or omissions of the parent or caretaker" [32]. In other words, these are cases in which there is reasonable cause to suspect child abuse and conduct an investigation.

Case Scenario

A young boy comes into the community health clinic for a physical exam. The boy's mother hovers and does not seem to want to let her son answer any questions. During the exam, in the process of taking blood, the nurse notices some bruises and lacerations on the boy's arm. Later, bruises in the shape of a belt are observed on the boy's back as well. Upon questioning, the boy will only say that he was "bad."

In this case, the nurse should make a report to ChildLine. This would be classified as a CPS case, and an investigation would be conducted. More information will be presented about reporting in later sections of this course.

GENERAL PROTECTIVE SERVICES

GPS is involved in non-abuse cases or acts that involve "non-serious injury or neglect" [38]. This includes children who experience "inadequate shelter, food, clothing, health care, truancy, inappropriate discipline, lack of supervision, hygiene issues, abandonment, or other problems that threaten a child's opportunity for healthy growth and development" [38]. One of the following criteria must be met for GPS to be involved [55]:

- Lack of parental control
- Deprivation of the essentials of life
- Illegal placement for adoption or care
- Abandonment by parents or guardians
- Chronic truancy
- Habitual disobedience

- Formal adjudication
- Commitment of a delinquent act at an age younger than 10 years
- Defined as ungovernable
- Born to parents with terminated parental rights

Case Scenario

Ms. J, a neighbor, notices E (5 years of age) and S (6 years of age) running around their front yard at 8 p.m. The front door of the house is wide open, and Ms. J asks if their mother is home. S states that her mother went out with her girlfriend to a party. Ms. J asks if a babysitter is at the house, and S answers "no" again. This is not the first time neighbors have noticed that the kids are left at home alone. The neighbors report that the mother often comes home late, intoxicated.

In this case, a bystander (likely Ms. J or one of the neighbors) could call ChildLine, the local county agency, or even the police, and the case would be addressed by GPS. More information will be presented about reporting in later sections of this course.

DEFINITIONS OF CHILD ABUSE AND NEGLECT

The federal definition of child abuse is evident in CAPTA, published as a product of federal legislation. CAPTA defines a child to be any individual younger than 18 years of age, except in cases of sexual abuse. In cases of sexual abuse, the age specified by the child protection laws varies depending on the state in which the child resides [5]. CAPTA defines child abuse as, "any recent act or failure to act on the part of a parent or caretaker, which results in death, serious physical or emotional harm, sexual abuse, or exploitation, or an act or failure to act that presents an imminent risk of serious harm" [6].

In Pennsylvania, the child abuse law takes a very comprehensive approach to defining of child abuse [26]. According to Pennsylvania law, child abuse refers to intentionally, knowingly, or recklessly doing any of the following [43; 54]:

- Causing bodily injury to a child through any recent act or failure to act
- Fabricating, feigning, or intentionally exaggerating or inducing a medical symptom or disease that results in a potentially harmful medical evaluation or treatment to the child through any recent act
- Causing or substantially contributing to serious mental injury to a child through any act or failure to act or a series of such acts or failures to act
- Causing sexual abuse or exploitation of a child through any act or failure to act
- Creating a reasonable likelihood of bodily injury to a child through any recent act or failure to act
- Creating a likelihood of sexual abuse or exploitation of a child through any recent act or failure to act
- Causing serious physical neglect of a child
- Engaging in any of the following recent acts:
  - Kicking, biting, throwing, burning, stabbing, or cutting a child in a manner that endangers the child
  - Unreasonably restraining or confining a child, based on consideration of the method, location, or duration of the restraint or confinement
  - Forcefully shaking a child younger than 1 year of age
  - Forcefully slapping or otherwise striking a child younger than 1 year of age
  - Interfering with the breathing of a child
  - Causing a child to be present at a location while a violation relating to the operation of methamphetamine laboratory is occurring, provided that the violation is being investigated by law enforcement
  - Leaving a child unsupervised with an individual, other than the child's parent, who the actor knows or reasonably should have known a) is required to register as a Tier II or Tier III sexual offender, where the victim of the sexual offense was younger than 18 years of age when the crime was committed; b) has been determined to be a sexually violent predator; or c) has been determined to be a sexually violent delinquent child
- Causing the death of the child through any act or failure to act
- Engaging a child in a severe form of trafficking in persons or sex trafficking, as those terms are defined under section 103 of the Trafficking Victims Protection Act of 2000

In addition, the Code explicitly excludes specific acts and injuries from the definition of child abuse. Effective December 31, 2014, the following are considered exclusions to the definition of child abuse [44]:

- Environmental factors: No child shall be deemed to be physically or mentally abused based on injuries that result solely from environmental factors, such as inadequate housing, furnishings, income, clothing, and medical care, that are beyond the control of the parent or person responsible for the child's welfare with whom the child resides. This shall not apply to any childcare service, excluding an adoptive parent.

- Practice of religious beliefs: If, upon investigation, the county agency determines that a child has not been provided needed medical or surgical care because of sincerely held religious beliefs of the child's parents or relative within the third degree of consanguinity and with whom the child resides, which beliefs are consistent with those of a bona fide religion, the child shall not be deemed to be physically or mentally abused. In such cases the following shall apply:
  - The county agency shall closely monitor the child and the child's family and shall seek court-ordered medical intervention when the lack of medical or surgical care threatens the child's life or long-term health.
  - All correspondence with a subject of the report and the records of the department and the county agency shall not reference child abuse and shall acknowledge the religious basis for the child's condition.
  - The family shall be referred for general protective services, if appropriate.
  - This subsection shall not apply if the failure to provide needed medical or surgical care causes the death of the child.
  - This subsection shall not apply to any child-care service as defined in this chapter, excluding an adoptive parent.
- Use of force for supervision, control, and safety purposes: Subject to the rights of parents, the use of reasonable force on or against a child by the child's own parent or person responsible for the child's welfare shall not be considered child abuse if any of the following conditions apply:
  - The use of reasonable force constitutes incidental, minor, or reasonable physical contact with the child or other actions that are designed to maintain order and control.
  - The use of reasonable force is necessary to quell a disturbance or remove the child from the scene of a disturbance that threatens physical injury to persons or damage to property; to prevent the child from self-inflicted physical harm; for self-defense or the defense of another individual; or to obtain possession of weapons or other dangerous objects or controlled substances or paraphernalia that are on the child or within the control of the child.
- Rights of parents: Nothing in this chapter shall be construed to restrict the generally recognized existing rights of parents to use reasonable force on or against their children for the purposes of supervision, control, and discipline of their children. Such reasonable force shall not constitute child abuse.
- Participation in events that involve physical contact with child: An individual participating in a practice or competition in an interscholastic sport, physical education, recreational activity, or extracurricular activity that involves physical contact with a child does not, in itself, constitute contact that is subject to the reporting requirements of this chapter.
- Defensive force: Reasonable force for self-defense or the defense of another individual shall not be considered child abuse.
  - Child-on-child contact: Harm or injury to a child that results from the act of another child shall not constitute child abuse unless the child who caused the harm or injury is a perpetrator. Notwithstanding this, the following shall apply: Acts constituting any of the following crimes against a child shall be subject to the reporting requirements: rape, involuntary deviate sexual intercourse, sexual assault, aggravated indecent assault, indecent assault, and indecent exposure.
  - No child shall be deemed to be a perpetrator of child abuse based solely on physical or mental injuries caused to another child in the course of a dispute, fight, or scuffle entered into by mutual consent.
  - A law enforcement official who receives a report of suspected child abuse is not required to make a report to the department if the person allegedly responsible for the child abuse is a nonperpetrator child.

It is important to note that exclusions are utilized by the CPS agency when investigating suspected abuse and should not be considered exclusions from reporting suspected abuse.

For the purposes of this course, a perpetrator is defined as a person who has committed child abuse. According to the Pennsylvania Code, the term includes only [42; 54]:

- A parent of the child
- A spouse or former spouse of the child's parent
- A paramour or former paramour of the child's parent
- A person 14 years of age or older and responsible for the child's welfare, including a person who provides temporary or permanent care, supervision, mental health diagnosis or treatment, or training or control of a child in lieu of parental care, supervision, and control
- An individual 14 years of age or older who resides in the same home as the child
- An individual 18 years of age or older who does not reside in the same home as the child but is related within the third degree of consanguinity or affinity by birth or adoption to the child

- An individual 18 years of age or older who engages a child in severe forms of trafficking in persons or sex trafficking, as those terms are defined under section 103 of the Trafficking Victims Protection Act of 2000

In a significant revision to the definition of perpetrator, school personnel and other childcare providers are considered "individuals responsible for the child's welfare" and may be perpetrators of child abuse; there is no longer a separate definition for student abuse [42]. As such, a perpetrator may be any such person who has direct or regular contact with a child through any program, activity, or services sponsored by a school, for-profit organization, or religious or other not-for-profit organization.

In addition, only the following may be considered a perpetrator for failing to act [42; 54]:

- A parent of the child
- A spouse or former spouse of the child's parent
- A paramour or former paramour of the child's parent
- A person 18 years of age or older and responsible for the child's welfare or who resides in the same home as the child

FORMS OF CHILD ABUSE AND NEGLECT

There are several acts that may be considered abusive, and knowledge of what constitutes abuse is vital for healthcare providers and other mandated reporters. In this section, specific behaviors that fall under the category of abuse and neglect will be reviewed.

Bodily Injury

Bodily injury, or physical abuse injuries, can range from minor bruises and lacerations to severe neurologic trauma and death. Physical abuse is one of the most easily identifiable forms of abuse and the type most commonly seen by healthcare professionals. Physical injuries that may be indicative of abuse include bruises/welts, burns, fractures, abdominal injuries, lacerations/abrasions, and central nervous system trauma [8; 34].

Bruises and welts are of particular concern, especially those that appear on:

- The face, lips, mouth, ears, eyes, neck, or head
- The trunk, back, buttocks, thighs, or extremities
- Multiple body surfaces

Patterns such as the shape of the article (e.g., a cord, belt buckle, teeth, hand) used to inflict the bruise or welt are common. Cigar or cigarette burns may be present, and they will often appear on the child's soles, palms, back, or buttocks. Patterned burns that resemble shapes of appliances, such as irons, burners, or grills, are of concern as well.

Fractures that result from abuse might be found on the child's skull, ribs, nose, or any facial structure. These may be multiple or spiral fractures at various stages of healing. When examining patients, note bruises on the abdominal wall, any intestinal perforation, ruptured liver or spleen, and blood vessel, kidney, bladder, or pancreatic injury, especially if accounts for the cause do not make sense. Look for signs of abrasions on the child's wrists, ankles, neck, or torso. Lacerations might also appear on the child's lips, ears, eyes, mouth, or genitalia. If violent shaking or trauma occurred, the child might experience a subdural hematoma [8; 34].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American College of Radiology, fractures highly suggestive of physical abuse include rib fractures, classic metaphyseal lesions, those unsuspected or inconsistent with the history or age of the child, multiple fractures involving more than one skeletal area, and fractures of differing ages.

(https://acsearch.acr.org/docs/69443/Narrative. Last accessed July 26, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Sexual Abuse/Exploitation

According to the Pennsylvania Code, sexual abuse or exploitation is defined as [45]:

- The employment, use, persuasion, inducement, enticement, or coercion of a child to engage in or assist another individual to engage in sexually explicit conduct, which includes, but is not limited to, the following:
  - Looking at the sexual or other intimate parts of a child or another individual for the purpose of arousing or gratifying sexual desire in any individual
  - Participating in sexually explicit conversation either in person, by telephone, by computer, or by a computer-aided device for the purpose of sexual stimulation or gratification of any individual
  - Actual or simulated sexual activity or nudity for the purpose of sexual stimulation or gratification of any individual
  - Actual or simulated sexual activity for the purpose of producing visual depiction, including photographing, videotaping, computer depicting, or filming

- Any of the following offenses committed against a child:
  - Rape
  - Statutory sexual assault
  - Involuntary deviate sexual intercourse
  - Sexual assault
  - Institutional sexual assault
  - Aggravated indecent assault
  - Indecent assault
  - Indecent exposure
  - Incest
  - Prostitution
  - Sexual abuse
  - Unlawful contact with a minor
  - Sexual exploitation

This does not include consensual activities between a child who is 14 years of age or older and another person who is 14 years of age or older and whose age is within four years of the child's age.

Child sexual abuse can be committed by a stranger or an individual known to the child. Sexual abuse may be manifested in many different ways, including [9; 10]:

- Verbal: Obscene phone calls or talking about sexual acts for the purpose of sexually arousing the adult perpetrator
- Voyeurism: Watching a child get dressed or encouraging the child to masturbate while the perpetrator watches
- Child prostitution: Involving the child in sexual acts for monetary profit
- Child pornography: Taking photos of a child in sexually explicit poses or acts
- Exhibitionism: Exposing his/her genitals to the child or forcing the child to observe the adult or other children in sexual acts
- Molestation: Touching, fondling, or kissing the child in a provocative manner; for example, fondling the child's genital area or long, lingering kisses
- Sexual penetration: The penetration of part of the perpetrator's body (e.g., finger, penis, tongue) into the child's body (e.g., mouth, vagina, anus)
- Rape: Usually involves sexual intercourse without the victim's consent and usually involves violence or the threat of violence
- Commercial sex act: Any sex act on account of which anything of value is given to or received by any person

Serious Physical Neglect

Pennsylvania law defines serious physical neglect of a child as repeated, prolonged, or egregious failure to supervise a child in a manner that is appropriate considering the child's developmental age and abilities, and/or the failure to provide a child with adequate essentials of life, including food, shelter, or medical care, when committed by a perpetrator that endangers a child's life or health, threatens a child's well-being, causes bodily injury, or impairs a child's health, development, or functioning. Due to the ambiguity of definitions of child abuse and neglect, CAPTA provides minimum standards that each state must incorporate in its definition of neglect. Examples of child neglect may include [6; 11; 12]:

- Failure to provide adequate food, clothing, shelter, hygiene, supervision, and protection
- Refusal and/or delay in medical attention and care (e.g., failure to provide needed medical attention as recommended by a healthcare professional or failure to seek timely and appropriate medical care for a health problem)
- Abandonment, characterized by desertion of a child without arranging adequate care and supervision. Children who are not claimed within two days or who are left alone with no supervision and without any information about their parents'/caretakers' whereabouts are examples of abandonment.
- Expulsion or blatant refusals of custody on the part of parent/caretaker, such as ordering a child to leave the home without adequate arrangement of care by others
- Inadequate supervision (i.e., child is left unsupervised or inadequately supervised for extended periods of time)

Serious Mental Injury

Under Pennsylvania law, serious mental injury (or emotional or psychological abuse) involves an act or failure to act by a perpetrator that causes nonaccidental serious mental injury. Serious mental injury is "a psychological condition, as diagnosed by a physician or licensed psychologist, including the refusal of appropriate treatment, that renders a child chronically and severely anxious, agitated, depressed, socially withdrawn, psychotic, or in reasonable fear that his or her life or safety is threatened, or that seriously interferes with a child's ability to accomplish age-appropriate development and social tasks" [45].

The following behaviors could constitute emotional abuse [6; 11; 12]:

- Verbal abuse: Belittling or making pejorative statements in front of the child, which results in a loss or negative impact on the child's self-esteem or self-worth
- Inadequate nurturance/affection: Inattention to the child's needs for affection and emotional support

- Witnessing domestic violence: Chronic spousal abuse in homes where the child witnesses the violence
- Substance and/or alcohol abuse: The parent/caretaker is aware of the child's substance misuse problem but chooses not to intervene or allows the behavior to continue
- Refusal or delay of psychological care: Failure or delay in obtaining services for the child's emotional, mental, or behavioral impairments
- Permitted chronic truancy: The child averages at least five days per month of school absence and the parent/guardian does not intervene
- Failure to enroll: Failure to enroll or register a child of mandatory school age or causing the child to remain at home for nonlegitimate reasons
- Failure to access special education services: Refusal or failure to obtain recommended services or |treatment for remedial or special education for a child's diagnosed learning disorder

Trafficking and Exploitation

It can be difficult to identify and intervene to stop human trafficking and exploitation, because it is hidden and even people who interact with victims may not recognize that it is happening. However, in many cases, women and children are considered the typical victims of human trafficking. Trafficking and exploitation are real risks to child safety and well-being and are reportable as forms of abuse.

There are several different types of child or minor human trafficking, but the term is generally defined as the recruitment, transportation, provision, or obtaining of a child for labor or services through the use of force, fraud, or coercion. Severe forms of human trafficking include sex and labor trafficking, including debt bondage and slavery.

Labor Trafficking

Labor trafficking is defined as labor obtained by the use of threat of serious harm, physical restraint, or abuse of the legal process. Severe labor trafficking includes the recruitment, harboring, transportation, provision, or obtaining of a person for labor or services, through the use of force, fraud, or coercion, for the purpose of subjection to involuntary servitude, peonage (i.e., paying off debt through work), debt bondage (i.e., debt slavery, bonded labor or services for a debt or other obligation), or slavery (i.e., a condition compared to that of a slave in respect of exhausting labor or restricted freedom).

Typically, children involved in forced labor are being given little or no pay. In the United States, forced labor is predominantly found in five sectors [57]:

- Prostitution and sex industry (46%)
- Domestic servitude (27%)
- Agriculture (10%)
- Sweatshops and factories (5%)
- Restaurant and hotel work (4%)

Among child victims, forced domestic servitude is a serious concern, particularly related to the provision of domestic services for 10 to 16 hours per day on activities such as child care, cooking, cleaning, and yard work/gardening.

Sex Trafficking

The Victims of Trafficking and Violence Protection Act defines sex trafficking as, "the recruitment, harboring, transportation, provision, or obtaining of a person for the purpose of a commercial sex act" [58]. A commercial sex act is, "any sex act on account of which anything of value is given to or received by any person" [58]. In other words, it involves the illegal transport of humans to be exploited in a sexual manner for financial gains [59]. Victims of sex trafficking could be forced into prostitution, stripping, pornography, escort services, and other sexual services [60]. Under federal law, sex trafficking (such as prostitution, pornography, or exotic dancing) does not require there be force, fraud, or coercion if the victim is younger than 18 years of age.

The term "domestic minor sex trafficking" has become a popular term used to connote the buying, selling, and/or trading of children for sexual services within the country, not internationally [60]. In the United States, the children most vulnerable to domestic minor trafficking are [60]:

- Youth in the foster care system
- Youth who identify as LGBTQIA+
- Youth who are homeless or runaway
- Youth with disabilities
- Youth with mental health or substance abuse disorders
- Youth with a history of sexual abuse
- Youth with a history of being involved in the welfare system
- Youth who identify as native or aboriginal
- Youth with family dysfunction

EPIDEMIOLOGY OF CHILD ABUSE AND NEGLECT

NATIONAL PREVALENCE

In 2020, there were 3.9 million referrals to child protective agencies in the United States [15]. More than 2.1 million (or 54%) were assessed to be appropriate for a response, and 27.6% of reports were made by health, social service, and/or mental health professionals [15]. Girls tend to be victims at a slightly higher rate (8.9 per 1,000 population) compared with boys (7.9 per 1,000 population) [15]. The most common perpetrators were parents; 90.6% of victims are maltreated by one or both

CHILD ABUSE VICTIMIZATION IN THE UNITED STATES ACCORDING TO RACE/ETHNICITY, 2020	
Race/Ethnicity	**Child Abuse Rate per 1,000 Children**
Native American/Alaska Native	15.5
African American	13.2
Multi-race	10.3
Pacific Islander	9.0
Hispanic	7.8
White	7.4
Asian American	1.6
Source: [15]	*Table 1*

parents [15]. Specifically, mothers are more often perpetrators compared with fathers (58.3% of victims were abused by a mother vs. 44.3% of victims were abused by a father) [15].

As of 2020, 8.4 of every 1,000 children in the United States were victims of abuse and/or neglect [15]. This is the unique rate, meaning each child is counted only once regardless the number of times a report may have been filed for abuse/neglect. The fatality rate for 2020 was 2.38 deaths per 100,000 children [15].

Research has shown that racial and ethnic minority children (particularly African American, Native American/Alaska Native, and multi-racial children) tend to have higher rates of reported child maltreatment compared with their White counterparts (***Table 1***) [15]. However, the lowest reported rate is among Asian American children [15].

PENNSYLVANIA STATE PREVALENCE

According to the Annual Child Protective Services Report, a yearly statistical report that documents child abuse cases in Pennsylvania, the child abuse hotline registered a total of 39,093 reports of suspected abuse or neglect in 2022 [27]. Approximately 12.8% of these cases were substantiated, which translates to 4,992 cases of child abuse in 2022 [27]. This is an increase of 6,174 reports (18.7%) compared with 2020, a decline attributed to the end of COVID-19 precautions and the return to usual contact between children and mandated reporters [27]. Of the substantiated child abuse cases, there were 60 fatalities, 13 less than in 2020 [27]. More than half (50.1%) of perpetrators of child abuse in 2022 were the parent of the child victim [27].

RECOGNIZING WARNING SIGNS

It is crucial that practitioners become familiar with the indications of child abuse and neglect. These factors do not necessarily conclusively indicate the presence of abuse or neglect; rather, they are clues that require further interpretation and clinical investigation. Some parental risk indicators include [8; 10; 12; 16]:

- Recounting of events that do not conform either with the physical findings or the child's physical and/or developmental capabilities
- Inappropriate delay in bringing the child to a health facility
- Unwillingness to provide information or the information provided is vague
- History of family violence in the home
- Parental misuse of substances and/or alcohol
- Minimal knowledge or concern about the child's development and care
- Environmental stressors, such as poverty, single parenthood, unemployment, or chronic illness in the family
- Unwanted pregnancy
- Early adolescent parent
- Expression that the parent(s) wanted a baby in order to feel loved
- Unrealistic expectations of the child
- Use of excessive physical punishment
- Healthcare service "shopping"
- History of parent "losing control" or "hitting too hard"

Child risk indicators include [8; 10; 12; 16]:

- Multiple school absences
- Learning or developmental disabilities
- History of multiple, unexplained illnesses, hospitalizations, or accidents
- Poor general appearance (e.g., fearful, poor hygiene, malnourished appearance, inappropriate clothing for weather conditions)
- Stress-related symptoms, such as headaches or stomachaches

- Frozen watchfulness
- Mental illness or symptoms, such as psychosis, depression, anxiety, eating disorders, or panic attacks
- Regression to wetting and soiling
- Sexually explicit play
- Excessive or out-of-the-ordinary clinging behavior
- Difficulties with concentration
- Disruptions in sleep patterns and/or nightmares

In addition, warning signs specifically associated with victims of child trafficking and/or exploitation include (but are not limited to):

- A youth that has been verified to be younger than 18 years of age and is in any way involved in the commercial sex industry or has a record of prior arrest for prostitution or related charges
- An explicitly sexual online profile
- Excessive frequenting of Internet chat rooms or classified sites
- Depicting elements of sexual exploitation in drawing, poetry, or other modes of creative expression
- Frequent or multiple sexually transmitted infections or pregnancies
- Lying about or not being aware of their true age
- Having no knowledge of personal data (e.g., age, name, date of birth)
- Having no identification
- Wearing sexually provocative clothing
- Wearing new clothes of any style, getting hair and/or nails done with no financial means
- Being secretive about whereabouts
- Having late nights or unusual hours
- Having a tattoo that s/he is reluctant to explain
- Being in a controlling or dominating relationship
- Not having control of own finances
- Exhibiting hypervigilance or paranoid behaviors
- Expressing interest in or being in relationships with adults or much older men or women

Some of the types of behaviors and symptoms discussed in the definitions of physical, sexual, and emotional abuse/neglect are also warning signs. For example, any of the injuries that may result from physical abuse, such as a child presenting with bruises in the shape of electric cords or belt buckles, should be considered risk factors for abuse.

CONSEQUENCES OF CHILD ABUSE

The consequences of child abuse and neglect vary from child to child, and these differences continue as victims grow older. Several factors will mediate the outcomes, including the [17]:

- Severity, intensity, frequency, duration, and nature of the abuse and/or neglect
- Age or developmental stage of the child when the abuse occurred
- Relationship between the victim and the perpetrator
- Support from family members and friends
- Level of acknowledgment of the abuse by the perpetrator
- Quality of family functioning

In examining some of the effects of physical abuse, it is helpful to frame the consequences along a lifespan perspective [3]. During infancy, physical abuse can cause neurologic impairments. Most cases of infant head trauma are the result of child abuse [19]. Neurologic damage may also affect future cognitive, behavioral, and developmental outcomes. Some studies have noted that, in early childhood, physically abused children show less secure attachments to their caretakers compared to their non-abused counterparts [20].

By middle to late childhood, the consequences are more notable. Studies have shown significant intellectual and linguistic deficits in physically abused children [3]. Other environmental conditions, such as poverty, may also compound this effect. In addition, a number of affective and behavioral problems have been reported among child abuse victims, including anxiety, depression, low self-esteem, excessive aggressive behaviors, conduct disorders, delinquency, hyperactivity, and social detachment [3; 8; 10; 12].

Surprisingly, there has been little research on the effects of childhood physical abuse on adolescents [3]. However, differences have been noted in parents who abuse their children during adolescence rather than preadolescence. It appears that lower socioeconomic status plays a lesser role in adolescent abuse as compared with abuse during preadolescence [21]. In addition, parents who abuse their children during adolescence are less likely to have been abused as children themselves compared with those parents who abused their children during preadolescence [21]. It is believed that the psychosocial effects of physical abuse manifest similarly in late childhood and adolescence.

Research findings regarding the effects of childhood physical abuse on adult survivors indicate an increased risk for major psychiatric disorders, including depression, post-traumatic stress disorder, and substance abuse [36]. Some adult survivors function well socially and in terms of mental and physical health, even developing increased resilience as a result of their

experiences, while others exhibit depression, anxiety, post-traumatic stress, substance abuse, criminal behavior, violent behavior, and poor interpersonal relationships [3; 17; 46]. A meta-analysis found that adult survivors of child abuse were more likely to experience depression than non-abused counterparts, with the rates varying according to the type of abuse sustained (1.5-fold increase for physical child abuse, 2.11-fold increase for neglect, and 3-fold increase for emotional abuse) [24]. Similar results were found in a longitudinal study that compared a child welfare cohort to a group with no child welfare involvement. The child welfare group was twice as likely to experience moderate-to-severe depression and generalized anxiety compared with the control group [25]. There is some evidence that vulnerability to long-term effects of maltreatment in childhood may be at least partially genetically mediated [50].

Although not all adult survivors of sexual abuse experience long-term psychological consequences, it is estimated that 20% to 50% of all adult survivors have identifiable adverse mental health outcomes [23]. Possible psychological outcomes include [10]:

- Affective symptoms: Numbing, post-traumatic stress disorder, anxiety, depression, obsessions and compulsions, somatization
- Interpersonal problems: Difficulties trusting others, social isolation, feelings of inadequacy, sexual difficulties (e.g., difficulties experiencing arousal and orgasm), avoidance of sex
- Distorted self-perceptions: Poor self-esteem, self-loathing, self-criticism, guilt, shame
- Behavioral problems: Risk of suicide, substance abuse, self-mutilation, violence
- Increased risk-taking behaviors: Abuse of substances, cigarette smoking, sexual risk-taking

Adult male survivors of child sexual abuse are three times as likely to perpetrate domestic violence as non-victims. In addition, female survivors of child sexual abuse are more vulnerable to bulimia, being a victim of domestic violence, and alcohol use disorder [28].

In more recent years, research has focused on the impact of adverse childhood experiences (ACEs) in general. ACEs are defined as potentially traumatic experiences that affect an individual during childhood (before 18 years of age) and increase the risk for future health and mental health problems (including increased engagement in risky behaviors) as adults [47]. Abuse and neglect during childhood are clear ACEs, but other examples include witnessing family or community violence; experiencing a family member attempting or completing suicide; parental divorce; parental or guardian substance abuse; and parental incarceration [47]. Adults who experienced ACEs are at increased risk for chronic illness, impaired health, violence, arrest, and substance use disorder [28; 52].

REPORTING SUSPECTED CHILD ABUSE

Pennsylvania has a delineated process in place to facilitate the reporting of suspected child abuse. In addition, in 2014, Governor Corbett signed four new bills intended to streamline and clarify the child abuse reporting process in Pennsylvania. These bills were spurred by the Sandusky child sexual abuse case.

PERMISSIVE REPORTERS

There are two general categories of child abuse reporters: mandated reporters and permissive reporters. Permissive reporters are individuals who report an incident of suspected child abuse. These persons are not required to act or intervene in cases of suspected abuse. Put plainly, permissive reporters can report abuse while mandated reporters must report. However, it is important to note that any person is encouraged to report suspected child abuse or cause a report of suspected child abuse to be made to the department, county agency, or law enforcement, if that person has reasonable cause to suspect that a child is a victim of child abuse. Reasonable cause to suspect is a determination made based on training/experience and all known circumstances. Some indicators may be more apparent than others depending on the type of abuse and/or depending on the child's health, developmental level, and well-being. For example, some indicators may be visible on the child's body while other indicators may be present in the child's behaviors.

MANDATED REPORTERS

In Pennsylvania, a mandated reporter is required to make a report of suspected child abuse when he or she has reasonable cause to suspect that a child is a victim of child abuse if [48]:

- The mandated reporter comes into contact with the child in the course of employment, occupation, and practice of a profession or through a regularly scheduled program, activity, or service.
- The mandated reporter is directly responsible for the care, supervision, guidance, or training of the child, or is affiliated with an agency, institution, organization, school, regularly established church or religious organization, or other entity that is directly responsible for the care, supervision, guidance, or training of the child, regardless of the setting of the disclosure of abuse (within or outside of the reporter's professional role).
- A person makes a specific disclosure to the mandated reporter that an identifiable child is the victim of child abuse either within or outside of the reporter's professional role.
- An individual 14 years of age or older makes a specific disclosure to the mandated reporter (either within or outside of the reporter's professional role) that the individual has committed child abuse.

The mandated reporter is not required to interrogate the victim or identify the person responsible for the child abuse in order to make a report of suspected child abuse.

By law, individuals who come into contact with children on a frequent and consistent basis due to their work are legally required to report any suspected child abuse [39]. Mandated reporters in the state of Pennsylvania include, but are not limited to, [39]:

- Physicians (including osteopaths)
- Medical examiners
- Coroners
- Funeral directors
- Dentists
- Optometrists
- Chiropractors
- Podiatrists
- Interns
- Registered nurses
- Licensed practical nurses
- Hospital personnel engaged in the admission, examination, care, or treatment of persons
- Christian Science practitioners
- Members of the clergy
- School administrators
- School teachers
- School nurses
- Social services workers
- Day-care center workers or any other child-care or foster-care workers
- Mental health professionals
- Peace officers or law enforcement officials

Senate Bill 21 and House Bill 436 were two of the bills signed into law and enacted in 2014. These bills elucidate that mandated reporters are "to include anyone who comes in contact with a child, or is directly responsible for the care, supervision, guidance, or training of a child" [51]. Under this expanded definition, additional individuals who are also classified as mandatory reporters include [39]:

- A person licensed or certified to practice in any health-related field under the jurisdiction of the Department of State
- A school employee
- A foster parent
- An individual, paid or unpaid, who, on the basis of the individual's role as an integral part of a regularly scheduled program, activity, or service, accepts responsibility for a child
- An employee of a social services agency
- An employee of a public library
- Those who are supervised by mandated reporters
- An independent contractor with direct contact with children
- An attorney affiliated with an agency, institution, or organization that is responsible for the care, supervision, guidance, or control of children

It has long been debated whether attorneys should be included as mandated reporters. With this new definition, there is a seeming compromise, limiting the mandate to attorneys who are affiliated with an organization that is responsible for the care or supervision of children [37].

Privileged communication between any mandated reporter and his or her patient or client does not apply in cases of child abuse, and failure to report this information is considered a violation of the law [39]. There are exceptions: confidential communication made to an ordained member of the clergy (within the scope of 42 Pennsylvania CS §§ 5943), and confidential communications made to an attorney so long as they are within the scope of 42 Pennsylvania CS §§ 5916 (relating to confidential communications to attorney) and 5928 (relating to confidential communications to attorney), the attorney work product doctrine, or the rules of professional conduct for attorneys [39]. Notwithstanding any other provision of law, a mandated reporter who makes a report of suspected child abuse or who makes a report of a crime against a child to law enforcement officials shall not be in violation of the Mental Health Procedures Act by releasing information necessary to complete the report.

The Pennsylvania Code states that whenever a person is a mandated reporter in his or her capacity as a member of the staff of a medical or other public or private institution, school, facility, or agency, that person shall report immediately and immediately thereafter notify the person in charge of the institution, school, facility, or agency (or the designated agent) [48]. Upon notification, the person in charge or the designated agent is responsible for facilitating the cooperation of the institution, school, facility, or agency with the investigation of the report.

Not surprisingly, more than three-quarters (80%) of suspected child abuse reports are made by mandated reporters [27]. More specifically, the majority of child abuse reports come from mandated reporters in public/private social services agencies.

THE PROCESS OF REPORTING CHILD ABUSE IN PENNSYLVANIA

In Pennsylvania, mandated reports of potential child abuse (CPS or GPS cases) are made either in writing (through the online portal) or orally to ChildLine. The ChildLine is available seven days per week, 24 hours per day at 800-932-0313 or 412-473-2000. In 2020, ChildLine answered 163,215 calls, including suspected child abuse cases, referrals for GPS, and inquiries for general information to services [27]. Electronic

submission of suspected child abuse reports may be made in lieu of calling ChildLine.

All mandated reporters who report via telephone shall also make a written report, which may be submitted electronically, within 48 hours [51]. The written reports are made through the Child Welfare Information Solution (CWIS) Portal, available online at https://www.compass.state.pa.us/cwis. The written report will include all of the following information, if known [55]:

- The names and addresses of the child, the child's parents, and any other person responsible for the child's welfare
- Where the suspected abuse occurred
- The age and sex of each subject of the report
- The nature and extent of the suspected child abuse, including any evidence of prior abuse to the child or any sibling of the child
- The name and relationship of each individual responsible for causing the suspected abuse and any evidence of prior abuse by each individual
- Family composition
- The source of the report
- The name, telephone number, and e-mail address of the person making the report
- The actions taken by the person making the report, including collection of evidence, protective custody, or admission to hospital
- Any other information required by federal law or regulation
- Any other information that the department requires by regulation

According to Pennsylvania law, a person or official required to report cases of suspected child abuse may take or request photographs of the child who is subject to a report and, if clinically indicated, request a radiologic examination and other medical tests on the child [56]. If completed, medical summaries or reports of the photographs, x-rays, and relevant medical tests should be sent along with the written report or within 48 hours after a report is made electronically. Persons who have reasonable cause to suspect a child is a victim of child abuse are NOT required to identify the person responsible for the abuse in order to make a report of suspected child abuse.

Except as allowed by Pennsylvania law, reports made to CPS, including, but not limited to, report summaries of child abuse and any other information obtained, reports written, or photographs or X-rays taken concerning alleged instances of child abuse, shall be confidential. Mandated reporters must identify themselves when reporting [54]. However, their names are usually not released; only the Secretary of the Department of Human Services has this authority. If a mandated reporter so chooses, he/she can sign a consent form that gives consent to have his/her name released [54].

A specialist at ChildLine will interview the caller to determine what the next step should be. This includes assessing if the report will be forwarded to a county agency for investigation as CPS or GPS; if a report should be forward directly to law enforcement officials; or if the caller will be referred to local services [53].

For both GPS and CPS cases, the appropriate county agency is contacted immediately [35]. The county agency is then responsible for its investigation, completing both a "risk assessment" and a "safety assessment." In CPS cases, the agency sees and evaluates the child within 24 hours of receiving the report. The primary goal of the evaluations are to assess the nature and extent of the abuse reported; to evaluate the level of risk or harm if the child were to stay in the current living situation; and to determine action(s) needed to ensure the child's safety [53].

A GPS referral will be assessed for any further needs, and appropriate referrals for services may be made for the child and family. If it is a CPS case, further investigation will be conducted. During the investigation, the agency may take photographs of the child and his/her injuries for the files. All investigations must be completed within 30 days from the date the report is taken at ChildLine [27]. Mandated reporters have a right to know of the findings of the investigation and the services provided to the child and may follow the case [33].

SUBSTANCE USE EXPOSURE AND PLANS OF SAFE CARE

Healthcare professionals in Pennsylvania, including those involved in the delivery or care of an infant affected by substance use or withdrawal symptoms (including fetal alcohol spectrum disorder) or encountering infants younger than 1 year of age outside a hospital setting, are required to notify the Pennsylvania Department of Human Services so that a Plan of Safe Care can be developed. It is important to note that this notification is not considered a child abuse report. In this context, healthcare provider or professional is defined as a licensed hospital or healthcare facility or person who is licensed, certified, or otherwise regulated to provide healthcare services under the laws of Pennsylvania, including physicians, podiatrists, optometrists, psychologists, physical therapists, certified nurse practitioners, registered nurses, nurse midwives, physician assistants, chiropractors, dentists, pharmacists, or individuals accredited or certified to provide behavioral health services. This is a notable shift from the previous law, which limited notification to only cases including illegal substance use and included an exception to reporting if the pregnant woman was receiving active treatment for a substance use disorder.

In 2019, the Pennsylvania Department of Health, Pennsylvania Department of Drug and Alcohol Programs, and Pennsylvania Department of Human Services published the Pennsylvania Plan of Safe Care Guidance addressing a framework for responding to the health and substance use disorder treatment needs of infants born affected by substance use disorder

and/or withdrawal symptoms and affected family or caregivers [65]. This publication includes definitions and evidence-based screening tools, based on standards of professional practice, to be utilized by healthcare providers to identify a child born affected by substance use or withdrawal symptoms resulting from prenatal drug exposure or a fetal alcohol spectrum disorder. The plan of safe care typically includes [65]:

- A release of information to allow for the collaboration among entities
- Referrals to treatment programs, mobile engagement and peer recovery specialists
- Education on neonatal abstinence syndrome, effects of substance use during pregnancy, and reporting requirements for substance exposed infants
- A relapse plan that includes child safety considerations and identified family supports
- Coordination between the obstetrician and the prescribing practitioner(s)
- Development of a birth plan, including pain management options
- Education and guidance on breastfeeding and substance use
- Stigma-reducing practices designed to engage the patient in consistent prenatal care
- Referrals to Family Strengthening, Early Head Start, Family Check Up for Children, Healthy Families America, Nurse-Family Partnership, Parents as Teachers, Family Group Decision Making (FGDM), Women Infant Children (WIC), public assistance, transportation assistance, counseling, housing assistance, domestic violence programs, and/or food banks
- Referral to ChildLine if there are concerns with mother's ability to be a caretaker for other children

After notification of a child born affected by substance use or withdrawal symptoms resulting from prenatal drug exposure or a fetal alcohol spectrum disorder, a multidisciplinary team meeting will be held prior to the child's discharge from the healthcare facility. For the purpose of informing the plan of safe care, this team may include public health agencies, maternal and child health agencies, home visitation programs, substance use disorder prevention and treatment providers, mental health providers, public and private children and youth agencies, early intervention and developmental services, courts, local education agencies, managed care organizations and private insurers, and hospitals and medical providers. The meeting will inform an assessment of the needs of the child and the child's parents and immediate caregivers to determine the most appropriate lead agency for developing, implementing, and monitoring a plan of safe care. The child's parents and immediate caregivers must be engaged to identify the need for access to treatment for any substance use disorder or other physical or behavioral health condition that may impact the safety, early childhood development, and well-being of the child.

Depending upon the needs of the child and parent(s)/caregiver(s), ongoing involvement of the county agency may not be required.

PROTECTIONS FOR REPORTERS

Reporters are afforded protections after reporting a suspected incidence of child abuse. Any person or institution who, in good faith, makes a report of child abuse, cooperates with a child abuse investigation, or testifies in a child abuse proceeding is considered immune from civil and criminal liability [44]. Mandated reporters who make a report in good faith and then later face discrimination in their workplace can take legal action [44]. (This protection from discrimination does not apply to an individual making a report who is found to be a perpetrator or to any individual who fails to make a required report.) For the most part, the reporter's identity is kept confidential. If a case is referred to law enforcement, then the name of the reporter must be given upon request; however, reporters are treated as confidential informants [49].

PENALTIES FOR FAILURE TO REPORT

According to Pennsylvania statutes, a person or official required to report a case of suspected child abuse or to make a referral to the appropriate authorities who willfully fails to do so commits a misdemeanor of the third degree for the first violation and a misdemeanor of the second degree for a second or subsequent violation [44; 54]. An offense is a felony of the third degree if all three of the following are true:

- The person or official willfully fails to report.
- The child abuse constitutes a felony of the first degree or higher.
- The person or official has direct knowledge of the nature of the abuse.

A person who commits a second or subsequent offense commits a felony of the third degree, except if the child abuse constitutes a felony of the first degree or higher, in which case the penalty for the second or subsequent offenses is a felony of the second degree. In addition, if a person's willful failure continues while the person knows or has reasonable cause to believe the child is actively being subjected to child abuse, the person commits a felony of the third degree; if the child abuse constitutes a felony of the first degree or higher, the person commits a felony of the second degree [44; 54]. The statute of limitations for an offense under this section shall be either the statute of limitations for the crime committed against the minor child or five years, whichever is greater.

BARRIERS TO REPORTING

Studies have shown that many professionals who are mandated to report child abuse and neglect are concerned and/or anxious about reporting. Identified barriers to reporting include [29; 30; 31; 40]:

- Professionals may not feel skilled in their knowledge base about child abuse and neglect. In addition, they lack the confidence to identify sexual and emotional abuse.
- Professionals may be frustrated with how little they can do about poverty, unemployment, drug use, and the intergenerational nature of abuse.
- Although professionals understand their legal obligation, they may still feel that they are violating patient confidentiality.
- Many professionals are skeptical about the effectiveness of reporting child abuse cases given the bureaucracy of the child welfare system.
- Practitioners may be concerned that they do not have adequate or sufficient evidence of child abuse.
- Practitioners may have a belief that government entities do not have the right to get involved in matters within the family.
- There may be some confusion and emotional distress in the reporting process.
- Practitioners may fear that reporting will negatively impact the therapeutic relationship.
- Some professionals have concerns that there might be negative repercussions against the child by the perpetrator.
- Some simply underestimate the seriousness and risk of the situation and may make excuses for the parents.

When interviewing children whose first language is not English, it is highly recommended that they be interviewed through the use of an interpreter. It can cause additional stress for children who struggle to find the right words in English, which can result in more feelings of fear, disempowerment, and voicelessness [41].

CASE SCENARIOS

In the following case scenarios, consider if the case should be reported as possible child abuse in accordance with Pennsylvania law.

A young girl, 2 years of age, is brought to the emergency department by her mother and stepfather for a scalp laceration. The girl is very quiet and appears listless and out of sorts. Her mother reports that she was injured when she fell onto a rock outside, but that the injury occurred when the girl was being watched by the stepfather. The girl undergoes assessment for traumatic brain injury, including assessment of function using the modified Glasgow Coma Score. The toddler is found to have mild impairment (a score of 13), and the follow-up test two hours later indicates normal functioning. The nurse notices that the toddler appears to be afraid of the stepfather, leaning away and crying when he is near her. The stepfather also appears to be easily frustrated with the child, saying that he does not know why she cries so much.

Aside from the physical injury, which could be consistent with the reported accident, this patient has some signs of bodily injury (e.g., flinches easily or avoids being touched) that may give a provider reasonable cause to suspect abuse. If the provider caring for this patient suspects that the stepfather may have neglected or physically abused her, they should make a report to ChildLine, which would initiate an investigation.

A boy, 13 years of age, is undergoing a routine physical exam with his family physician. The physician asks the boy if he is excited to start school in the next few weeks and how his baseball team is doing. The boy becomes quiet and states that he is nervous about an upcoming trip with his baseball team but does not give additional information. When asked directly, the boy says that he is uncomfortable with the new assistant coach, who watches pornography with them during out-of-town tournaments and supplies them with pornographic magazines. However, the boy states that he doesn't think it's a big deal and that "all of the other kids seem to really like it."

In this case, the physician should make a report to ChildLine. This would be classified as a CPS case, and an investigation would be conducted.

A girl, 6 years of age, visits the school nurse complaining of a stomach ache. She is disheveled in appearance, with torn, dirty clothing and unbrushed hair. She reports being hungry, as she did not have dinner the night before or breakfast this morning. She also reports that she has been sleeping in a car with her mother since they moved out of their apartment last month.

The signs in the case indicate poverty, not abuse. As such, a report should not be made to ChildLine. Instead, the patient and her family should be connected with available services and resources to assist in meeting their immediate needs.

CONCLUSION

Child abuse and neglect are considered significant social problems with deleterious consequences. As noted, a system has been implemented in all 50 states to ensure the safety of children, with laws defining what constitutes abuse and neglect and who is mandated to report. Healthcare professionals, regardless of their discipline or field, are in a unique position to assist in the identification, education, and prevention of child abuse and neglect. There are three key components of child abuse: a child victim and an act or failure to act (or series of acts or failures) engaged in intentionally, knowingly, or recklessly. The basis for reporting suspected child abuse is having reasonable

cause to suspect a child is a victim of abuse. A person who has reasonable cause to suspect a child is a victim of child abuse is not required to identify the type of abuse they are reporting when making a report.

A mandated reporter must immediately make a report suspected child abuse to ChildLine if they have reasonable cause to suspect a child is a victim of child abuse under any of the following circumstances:

- The mandated reporter comes into contact with the child in the course of employment, occupation, and practice of a profession or through a regularly scheduled program, activity, or service.
- The mandated reporter is directly responsible for the care, supervision, guidance, or training of the child, or is affiliated with an agency, institution, organization, school, regularly established church or religious organization, or other entity that is directly responsible for the care, supervision, guidance, or training of the child.
- A person makes a specific disclosure to the mandated reporter that an identifiable child is the victim of child abuse.
- An individual 14 years of age or older makes a specific disclosure to the mandated reporter that the individual has committed child abuse.

It is not necessary for a child to come before the mandated reporter in order for the mandated reporter to make a report of suspected child abuse. In addition, the mandated reporter is not required to identify the person responsible for the child abuse in order to make a report. A person who has reasonable cause to suspect a child is a victim of abuse does not have to consider the exclusions from child abuse in order to make a report of suspected abuse. A mandated reporter is presumed to have acted in good faith when making a report.

It is the duty of all mandated reporters in the state of Pennsylvania to know their responsibilities and the laws that govern the reporting process. All reporters should adhere to the established laws and rules that govern child abuse reporting, taking into account the expanded definition of perpetrator, the updated processes in place for reporting cases of suspected child abuse, and the delineated roles of mandated reporters. Doing so will help ensure the safety of millions of children in Pennsylvania.

RESOURCES

ChildLine: Pennsylvania Child Abuse Hotline
1-800-932-0313
https://www.dhs.pa.gov/keepkidssafe

Child Welfare Information Gateway
330 C Street SW
Washington, DC 20201
1-800-394-3366
To report abuse: 1-800-422-4453
https://www.childwelfare.gov

Child Welfare League of America
727 15th Street NW, 12th Floor
Washington, DC 20005
202-688-4200
https://www.cwla.org

National Council on Child Abuse and Family Violence
P.O. Box 5222
Arlington, VA 22205
202-429-6695
https://www.preventfamilyviolence.org

Pennsylvania Chapter of Children's Advocacy Centers and Multidisciplinary Teams
P.O. Box 3323
Erie, PA 16508
814-431-8151
https://penncac.org

Pennsylvania Child Welfare Information Solution
877-343-0494
https://www.compass.state.pa.us/cwis

Pennsylvania Department of Human Services
P.O. Box 2675
Harrisburg, PA 17105
1-800-692-7462
https://www.dhs.pa.gov

University of Pittsburgh, Pennsylvania Child Welfare Resource Center
403 East Winding Hill Road
Mechanicsburg, PA 17055
717-795-9048
http://www.pacwrc.pitt.edu

Customer Information/Answer Sheet/Evaluation insert located between pages 60–61.

TEST QUESTIONS

#97542 CHILD ABUSE IDENTIFICATION AND REPORTING: THE PENNSYLVANIA REQUIREMENT

This is an open book test. Please record your responses on the Answer Sheet.
A passing grade of at least 80% must be achieved in order to receive credit for this course.

This 3 Credit activity must be completed by July 31, 2025.

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1. The first child abuse case in the United States that garnered widespread interest involved Mary Ellen Wilson, a foster child in New York City. This case took place in
- *A) 1790.*
- *B) 1866.*
- *C) 1921.*
- *D) 1965.*

2. How is the child welfare system in Pennsylvania characterized?
- *A) It is monitored by CAPTA.*
- *B) The child welfare system is founded on the criminal justice model.*
- *C) It is supervised by the state and administered by the various local county agencies.*
- *D) It is supervised by each respective local county agency and administered by the federal government.*

3. Child abuse is defined at the federal level by the
- *A) Child Protective Services.*
- *B) Office of Child and Family Welfare.*
- *C) Child Abuse Prevention and Treatment Act.*
- *D) National Council on Child Abuse and Family Violence.*

4. Which of the following injuries is NOT considered a possible indicator of physical abuse?
- *A) Patterned burns*
- *B) Bruises on multiple body areas*
- *C) Abrasions to the knees and elbows*
- *D) Multiple or spiral fractures at various stages of healing*

5. Child sexual abuse is categorized as exhibitionism if the act involves
- *A) obscene phone calls.*
- *B) forcing a child to observe sexual acts.*
- *C) watching a child get dressed or undressed.*
- *D) touching, fondling, or kissing the child in a provocative manner.*

6. How many substantiated cases of child abuse occurred in Pennsylvania in 2022?
- *A) 280*
- *B) 1,967*
- *C) 4,992*
- *D) 26,944*

7. Patient A, a child 10 years of age, arrives at the emergency department with a burn. Upon intake, a registered nurse notices that the burn on the child's thigh resembles the face of an iron. In addition, the child has bruising on her upper arm. The nurse suspects abuse and therefore calls the toll-free number for mandated reporters to report the case. Which of the following steps must the nurse take following the call?
- *A) This nurse must report the suspected abuse in writing within 48 hours.*
- *B) The nurse must contact a physician for a complete evaluation of the child, including assessment for sexual abuse.*
- *C) The nurse should call a legal aid society to ask for a lawyer to represent her in the event he/she is held liable if the case is not substantiated.*
- *D) This nurse should inform the mother that he/she will be contacting the appropriate agencies regarding suspected child abuse and maltreatment.*

8. When making a written report of suspected child abuse, the mandated reporter may be asked for

A) family composition.
B) photographs of the injuries, if available.
C) the location where the suspected abuse occurred.
D) All of the above

9. The identity of the individual who reported a child abuse incident is NOT kept confidential if

A) the report is substantiated.
B) the incident is reported to law enforcement officials.
C) the intake specialist determines that the incident falls under general protective services.
D) the individual who reported the incident is determined to not have made the call in good faith.

10. A failure to report suspected child abuse by a mandated reporter is considered a felony of the third degree if

A) the person willfully fails to report.
B) the child abuse constitutes a felony of the first degree or higher.
C) the person has direct knowledge of the nature of the abuse.
D) All of the above

Be sure to transfer your answers to the Answer Sheet located on the envelope insert.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Intercultural Competence and Patient-Centered Care

In addition to receiving *AMA PRA Category 1 Credit™*, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board: 4 ABIM MOC Points, 4 ABS Points, 4 ABA MOC Points, 4 ABP MOC Points, 4 ABPath Points.

Audience
This course is designed for all members of the interprofessional healthcare team.

Course Objective
The purpose of this course is to provide members of the interprofessional healthcare team with the knowledge, skills, and strategies necessary to provide culturally competent and responsive care to all patients.

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

1. Define cultural competence, implicit bias, and related terminology.
2. Outline social determinants of health and barriers to providing care.
3. Discuss best practices for providing culturally competent care to various patient populations.
4. Discuss key aspects of creating a welcoming and safe environment, including avoidance of discriminatory language and behaviors.

Faculty
Alice Yick Flanagan, PhD, MSW, received her Master's in Social Work from Columbia University, School of Social Work. She has clinical experience in mental health in correctional settings, psychiatric hospitals, and community health centers. In 1997, she received her PhD from UCLA, School of Public Policy and Social Research. Dr. Yick Flanagan completed a year-long post-doctoral fellowship at Hunter College, School of Social Work in 1999. In that year she taught the course Research Methods and Violence Against Women to Masters degree students, as well as conducting qualitative research studies on death and dying in Chinese American families. (A complete biography can be found online at www.NetCE.com.)

Faculty Disclosure
Contributing faculty, Alice Yick Flanagan, PhD, MSW, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner
John M. Leonard, MD

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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This activity has been designated for 4 Lifelong Learning (Part II) credits for the American Board of Pathology Continuing Certification Program.

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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

Culturally competent care has been defined as "care that takes into account issues related to diversity, marginalization, and vulnerability due to culture, race, gender, and sexual orientation" [1]. A culturally competent person is someone who is aware of how being different from the norm can be marginalizing and how this marginalization may affect seeking or receiving health care [1]. To be effective cross-culturally with any diverse group, healthcare professionals must have awareness, sensitivity, and knowledge about the culture involved, enhanced by the use of cross-cultural communication skills [2; 3].

Healthcare professionals are accustomed to working to promote the healthy physical and psychosocial development and well-being of individuals within the context of the greater community. For years, these same professionals have been identifying at-risk populations and developing programs or making referrals to resources to promote the health and safety of at-risk groups. But, because of general assumptions, persistent stereotypes, and implicit and explicit biases, culture-related healthcare disparities persist [2]. In the increasingly diverse landscape of the United States, assessing and addressing culture-related barriers to care are a necessary part of health care. This includes seeking to improve one's cultural competence and identifying blind spots and biases.

DEFINITIONS

CULTURAL COMPETENCE

In healthcare, cultural competence is broadly defined as practitioners' knowledge of and ability to apply cultural information and appreciation of a different group's cultural and belief systems to their work [4]. It is a dynamic process, meaning that there is no endpoint to the journey to becoming culturally aware, sensitive, and competent. Some have argued that cultural curiosity is a vital aspect of this approach.

CULTURAL HUMILITY

Cultural humility refers to an attitude of humbleness, acknowledging one's limitations in the cultural knowledge of groups. Practitioners who apply cultural humility readily concede that they are not experts in others' cultures and that there are aspects of culture and social experiences that they do not know. From this perspective, patients are considered teachers of the cultural norms, beliefs, and value systems of their group, while practitioners are the learners [5]. Cultural humility is a lifelong process involving reflexivity, self-evaluation, and self-critique [6].

DISCRIMINATION

Discrimination has traditionally been viewed as the outcome of prejudice [7]. It encompasses overt or hidden actions, behaviors, or practices of members in a dominant group against members of a subordinate group [8]. Discrimination has also been further categorized as lifetime, which consists of major discreet discriminatory events, or everyday, which is subtle, continual, and part of day-to-day life and can have a cumulate effect on individuals [9].

DIVERSITY

Diversity "encompasses differences in and among societal groups based on race, ethnicity, gender, age, physical/mental abilities, religion, sexual orientation, and other distinguishing characteristics" [10]. Diversity is often incorrectly conceptualized into singular dimensions as opposed to multiple and intersecting diversity factors [11].

INTERSECTIONALITY

Intersectionality is a term to describe the multiple facets of identity, including race, gender, sexual orientation, religion, sex, and age. These facets are not mutually exclusive, and the meanings that are ascribed to these identities are inter-related and interact to create a whole [12]. This term also encompasses the ways that different types and systems of oppression intersect and affect individuals.

PREJUDICE

Prejudice is a generally negative feeling, attitude, or stereotype against members of a group [13]. It is important not to equate prejudice and racism, although the two concepts are related. All humans have prejudices, but not all individuals are racist. The popular definition is that "prejudice plus power equals racism" [13]. Prejudice stems from the process of ascribing every member of a group with the same attributes [14].

RACISM

Racism is the "systematic subordination of members of targeted racial groups who have relatively little social power...by members of the agent racial group who have relatively more social power" [15]. Racism is perpetuated and reinforced by social values, norms, and institutions.

There is some controversy regarding whether unconscious (implicit) racism exists. Experts assert that images embedded in our unconscious are the result of socialization and personal observations, and negative attributes may be unconsciously applied to racial minority groups [16]. These implicit attributes affect individuals' thoughts and behaviors without a conscious awareness.

Structural racism refers to the laws, policies, and institutional norms and ideologies that systematically reinforce inequities, resulting in differential access to services such as health care, education, employment, and housing for racial and ethnic minorities [17; 18].

BIAS: IMPLICIT AND EXPLICIT

In a sociocultural context, biases are generally defined as negative evaluations of a particular social group relative to another group. Explicit biases are conscious, whereby an individual is fully aware of his/her attitudes and there may be intentional behaviors related to these attitudes [19]. For example, an individual may openly endorse a belief that women are weak and men are strong. This bias is fully conscious and is made explicitly known. The individual's ideas may then be reflected in his/her work as a manager.

FitzGerald and Hurst assert that there are cases in which implicit cognitive processes are involved in biases and conscious availability, controllability, and mental resources are not [20]. The term "implicit bias" refers to the unconscious attitudes and evaluations held by individuals. These individuals do not necessarily endorse the bias, but the embedded beliefs/attitudes can negatively affect their behaviors [21; 22; 23; 24]. Some have asserted that the cognitive processes that dictate implicit and explicit biases are separate and independent [24].

Implicit biases can start as early as 3 years of age. As children age, they may begin to become more egalitarian in what they explicitly endorse, but their implicit biases may not necessarily change in accordance to these outward expressions [25]. Because implicit biases occur on the subconscious or unconscious level, particular social attributes (e.g., skin color) can quietly and insidiously affect perceptions and behaviors [26]. According to Georgetown University's National Center on Cultural Competency, social characteristics that can trigger implicit biases include [27]:

- Age
- Disability
- Education
- English language proficiency and fluency
- Ethnicity
- Health status
- Disease/diagnosis (e.g., human immunodeficiency virus [HIV])
- Insurance
- Obesity
- Race
- Socioeconomic status
- Sexual orientation, gender identity, or gender expression
- Skin tone
- Substance use

An alternative way of conceptualizing implicit bias is that an unconscious evaluation is only negative if it has further adverse consequences on a group that is already disadvantaged or produces inequities [20; 28]. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages [28].

When the concept of implicit bias was introduced in the 1990s, it was thought that implicit biases could be directly linked to behavior. Despite the decades of empirical research, many questions, controversies, and debates remain about the dynamics and pathways of implicit biases [21].

Specific conditions or environmental risk factors have been associated with an increased risk for certain implicit biases, including [130; 131]:

- Stressful emotional states (e.g., anger, frustration)
- Uncertainty
- Low-effort cognitive processing
- Time pressure
- Lack of feedback
- Feeling behind with work
- Lack of guidance
- Long hours
- Overcrowding
- High-crises environments
- Mentally taxing tasks
- Juggling competing tasks

ROLE OF INTERPROFESSIONAL COLLABORATION AND PRACTICE

The study of implicit bias is appropriately interdisciplinary, representing social psychology, medicine, health psychology, neuroscience, counseling, mental health, gerontology, gender/sexuality studies, religious studies, and disability studies [28]. Therefore, implicit bias empirical research and curricula training development lends itself well to interprofessional collaboration and practice (ICP).

The main characteristics of ICP allow for implicit and explicit biases to be addressed by the interprofessional team. One of the core features of ICP is sharing—professionals from different disciplines share their philosophies, values, perspectives, data, and strategies for planning of interventions [29]. ICP also involves the sharing of roles, responsibilities, decision making, and power [30]. Everyone on the team employs their expertise, knowledge, and skills, working collectively on a shared, patient-centered goal or outcome [30; 31].

Another feature of ICP is interdependency. Instead of working in an autonomous manner, each team member's contributions are valued and maximized, which ultimately leads to synergy [29]. At the heart of this are two other key features: mutual trust/respect and communication [31]. In order to share responsibilities, the differing roles and expertise are respected.

Experts have recommended that a structural or critical theoretical perspective be integrated into core competencies in healthcare education to teach students about implicit bias, racism, and health disparities [32]. This includes [32]:

- Values/ethics: The ethical duty for health professionals to partner and collaborate to advocate for the elimination of policies that promote the perpetuation of implicit bias, racism, and health disparities among marginalized populations.
- Roles/responsibilities: One of the primary roles and responsibilities of health profes-sionals is to analyze how institutional and organizational factors promote racism and implicit bias and how these factors contribute to health disparities. This analysis should extend to include one's own position in this structure.
- Interprofessional communication: Ongoing discussions of implicit bias, perspective taking, and counter-stereotypical dialogues should be woven into day-to-day practice with colleagues from diverse disciplines.
- Teams/teamwork: Health professionals should develop meaningful contacts with marginalized communities in order to better understand whom they are serving.

Adopting approaches from the fields of education, gender studies, sociology, psychology, and race/ethnic studies can help build curricula that represent a variety of disciplines [33]. Students can learn about and discuss implicit bias and its impact, not simply from a health outcomes perspective but holistically. Skills in problem-solving, communication, leadership, and teamwork should be included [33].

SOCIAL DETERMINANTS OF HEALTH

Social determinants of health are the conditions in the environments where people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks. These circumstances are shaped by the distribution of money, power, and resources at global, national, and local levels. Healthy People 2030 groups social determinants of health into five categories [34]:

- Economic stability
- Education access and quality
- Health care access and quality
- Social and community context
- Neighborhood and built environment

These factors have a major impact on people's health, well-being, and quality of life. Examples of social determinants of health include [34]:

- Safe housing, transportation, and neighborhoods
- Racism, discrimination, and violence
- Education, job opportunities, and income
- Access to nutritious foods and physical activity opportunities
- Polluted air and water
- Language and literacy skills

Social determinants of health also contribute to wide health disparities and inequities. For example, people who lack access to grocery stores with healthy foods are less likely to have good nutrition, which raises the risk of heart disease, diabetes, and obesity and lowers life expectancy compared with those who have easier access to healthy foods [34].

Promoting healthy choices will not eliminate these and other health disparities. Instead, public health organizations and their partners must take action to improve the conditions in people's environments. Healthcare providers play a role by identifying factors affecting the health of their patients, providing resources (when appropriate), and advocating for healthy environments.

ECONOMIC STABILITY

In the United States, 1 in 10 people live in poverty, and many people are unable afford healthy foods, health care, and housing. People with steady employment are less likely to live in poverty and more likely to be healthy, but many people have trouble finding and keeping a job. People with disabilities, injuries, or chronic conditions (e.g., arthritis) may be especially limited in their ability to work. In addition, many people with steady work still do not earn enough to afford the things they need to stay healthy [34].

Employment programs, career counseling, and high-quality childcare opportunities can help more people find and keep jobs. In addition, policies to help people pay for food, housing, health care, and education can reduce poverty and improve health and well-being [34].

HEALTH CARE ACCESS AND QUALITY

Many people in the United States are unable to access the healthcare services they need. About 1 in 10 people in the United States lack health insurance, and people without insurance are less likely to have a primary care provider and be able to afford the healthcare services and medications they need. Strategies to increase insurance coverage rates are critical for making sure more people get important healthcare services, including preventive care and treatment for chronic illnesses [34].

In some cases, patients are not recommended health care services (e.g., cancer screenings) because they do not have a primary care provider or because they live too far away from healthcare providers who offer them. Interventions to increase access to healthcare professionals and improve communication—in person or remotely—can help more people get the care they need [34].

SOCIAL AND COMMUNITY CONTEXT

People's relationships and interactions with family, friends, co-workers, and community members can have a major impact on their health and well-being. Many people face challenges and dangers they are not able to control, including unsafe neighborhoods, discrimination, or trouble affording the things they need. This can have a negative impact on health and safety throughout life.

Positive relationships at home, at work, and in the community can help reduce these negative impacts. But some people (e.g., children whose parents are in jail, adolescents who are bullied) often do not get support from loved ones or others. Interventions to help people access the social and community support they need are critical for improving health and well-being [34]. Healthy People 2030 objectives in this category focus on increasing the proportion of children and adolescents who have an adult they can talk to about serious problems, improving community health literacy, increasing the likelihood that an individual talks to friends or family about their health, and expanding access to online healthcare services [34].

BARRIERS TO PROVIDING CARE

Culturally diverse patients experience a variety of barriers when seeking health and mental health care, including:

- Immigration status
- Lower socioeconomic status
- Language barriers
- Cultural differences
- Lack of or poor health insurance coverage
- Fear of or experiences with provider discrimination
- Mistrust of healthcare systems

Such obstacles can interfere with or prevent access to treatment and services, compromise appropriate referrals, affect compliance with recommendations, and result in poor outcomes. Culturally competent providers build and maintain rich referral resources to meet patients' assorted needs.

Encountering discrimination when seeking health or mental health services is a barrier to optimal care and contributor to poorer outcomes in under-represented groups. Some providers will not treat patients because of moral objections, which can affect all groups, but particularly those who are gender and/or sexual minorities, religious minorities, and/or immigrants. In fact, in 2016, Mississippi and Tennessee passed laws allowing health providers to refuse to provide services if doing so would violate their religious beliefs [35]. However, it is important to remember that providers are obligated to act within their profession's code of ethics and to ensure patients receive the best possible care.

BEST PRACTICES FOR CULTURALLY RESPONSIVE CARE

The U.S. Department of Health and Human Services has outlined steps important to incorporate in evaluation and treatment planning processes to ensure culturally competent clinical and programmatic decisions and skills [36].

The first step is to engage patients. In nonemergent situations, it is important to establish rapport before asking a series of assessment questions or delving deeply into history taking. Providers should use simple gestures as culturally appropriate (e.g., handshakes, facial expressions, greetings) to help establish a first impression. The intent is that all patients feel understood and seen following each interaction. Culturally responsive interview behaviors and paperwork should be used at all times [36].

When engaging in any patient teaching, remember that individuals may be new to the specific language or jargon and expectations of the diagnosis and care process. Patients should be encouraged to collaborate in every step of their care. This consists of seeking the patient's input and interpretation and establishing ways they can seek clarification. Patient feedback can then be used to help identify cultural issues and specific needs. If appropriate, collaboration should extend to include family and community members.

Assessment should incorporate culturally relevant themes in order to more fully understand patients and identify their cultural strengths and challenges. Themes include [36]:

- Immigration history
- Cultural identity and acculturation
- Membership in a subculture
- Beliefs about health, healing, and help-seeking
- Trauma and loss

In some cases, it may be appropriate and beneficial to obtain culturally relevant collateral information, with the patient's permission, from sources other than the patient (e.g., family or community members) to better understand beliefs and practices that shape the patient's cultural identity and understanding of the world.

Practitioners should work to identify screening and assessment tools that have been translated into or adapted for other languages and have been validated for their particular population group(s). An instrument's cultural applicability to the population being served should be assessed, keeping in mind that research is limited on the cross-cultural applicability of specific test items or questions, diagnostic criteria, and concepts in evaluative and diagnostic processes [36].

Typically, culturally responsive care establishes holistic treatment goals that include objectives to improve physical health and spiritual strength; utilizes strengths-based strategies that fortify cultural heritage, identity, and resiliency; and recognizes that treatment planning is a dynamic process that evolves along with an understanding of patient history and treatment needs.

In addition to these general approaches, specific considerations may be appropriate for specific populations. While discussion of every possible patient subgroup is outside of the scope of this course, some of the most common factors are outlined in the following sections [36].

RACIAL BACKGROUNDS

Race and color impact the ways in which individuals interact with their environments and are perceived and treated by others. Race is defined as groups of humans divided on the basis of inherited physical and behavioral differences. As part of the cultural competence process and as a reflection of cultural humility, practitioners should strive to learn as much as possible about the specific racial/ethnic populations they serve [37]. However, considerable diversity exists within any specific culture, race, or ethnicity [37]. Cultural beliefs, traditions, and practices change over time, both through generations and within an individual's lifetime. It is also possible for the

differences between two members of the same racial/ethnic group to be greater than the differences between two people from different racial/ethnic groups. Within-group variations in how persons interact with their environments and specific social contexts are also often present.

As with all patients, it is vital to actively listen and critically evaluate patient relationships. All practitioners should seek to educate themselves regarding the experiences of patients who are members of a community that differs from their own. Resources and opportunities to collaborate may be available from community organizations and leaders.

Finally, preferred language and immigration/migration status should be considered. Interpreters should be used when appropriate, with adherence to best practices for the use of interpretation services. Stressing confidentiality and privacy is particularly important for undocumented workers or recent immigrants, who may be fearful of deportation.

Black Patients

"Black" or "African American" is a classification that serves as a descriptor; it has sociopolitical and self-identification ramifications. The U.S. Census Bureau defines African Americans or Black Americans as persons "having origins in any of the Black racial groups of Africa" [38].

According to the U.S. Census, African Americans number 46.9 million as of 2020 [39]. By 2060, it is projected they will comprise 17.9% of the U.S. population [40]. This group tends to be young; 30% of the African American population in the United States is younger than 18 years of age. In 2019, the median age for this group was 35 years [41]. In terms of educational attainment, 89.4% of African Americans 25 years of age or older had a high school diploma or completed college in 2020 [39]. Texas has the largest African American population, at 3.9 million [41].

Historical adversity and institutional racism contribute to health disparities in this group. For the Black population, patient assessment and treatment planning should be framed in a context that recognizes the totality of life experiences faced by patients. In many cases, particularly in the provision of mental health care, equality is sought in the provider-patient relationship, with less distance and more disclosing. Practitioners should assess whether their practices connect with core values of Black culture, such as family, kinship, community, and spirituality. Generalized or Eurocentric treatment approaches may not easily align with these components of the Black community [42]. Providers should also consider the impact of racial discrimination on health and mental health among Black patients. Reports indicate that expressions of emotion by Black patients tend to be negatively misunderstood or dismissed; this reflects implicit or explicit biases.

EVIDENCE-BASED PRACTICE RECOMMENDATION

When providing mental health services for African Americans, the American Psychiatric Association recommends exploring how a patient's present experiences connect to historical trauma for a particular group or community.

(https://www.psychiatry.org/psychiatrists/diversity/education/stress-and-trauma/african-americans. Last accessed September 26, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

Asian Patients

As of 2019, 22.9 million Americans identified as Asian [43]. Between 2000 and 2019, Asians experienced the greatest growth compared with any other racial group at 81% [44; 45]. The Chinese group represents the largest Asian subgroup in the United States, and it is projected that this population will grow to 35.7 million between 2015 and 2040 [46; 47]. In 2019, Chinese Americans (excluding Taiwanese Americans) numbered at 5.2 million [43]. They also have the highest educational attainment; 54.6% of Asians 25 years of age or older had a bachelor's degree or higher in 2019 [43].

"Asian" is a single term widely used to describe individuals who have kinship and identity ties to Asia, including the Far East, Southeast Asia, and the Indian subcontinent [48]. This encompasses countries such as China, Japan, Korea, Vietnam, Cambodia, Thailand, India, Pakistan, and the Philippines. Pacific Islander is often combined with Asian American in census data. The Pacific Islands include Hawaii, Guam, Samoa, Fiji, and many others [48]. There are more than 25 Asian/Pacific Islander groups, each with a different migration history and widely varying sociopolitical environments in their homelands [49].

Asian American groups have differing levels of acculturation, lengths of residency in the United States, languages, English-speaking proficiency, education attainment, socioeconomic statuses, and religions. For example, there are approximately 32 different languages spoken among Asian Americans, and within each Asian subgroup (e.g., Chinese), multiple dialects may be present [49; 50]. In 2019, California had the largest Asian American population, totaling 5.9 million [44].

Recommended best practices when caring for Asian American patients include:

- Create an advisory committee using representatives from the community.
- Incorporate cultural knowledge and maintain flexible attitudes.
- Provide services in the patients' primary language.

- Develop culturally specific questionnaires for intake to capture information that may be missed by standard questionnaires.
- Emphasize traditional values and incorporate traditional practices (e.g., acupuncture) into treatment plans, when appropriate and desired.
- Explore patient coping mechanisms that draw upon cultural strengths.

Latino/a/x or Hispanic Patients

In 2020, the Hispanic population in the United States numbered 60.6 million [51]. The majority of the Hispanic population in the United States (63.3%) identify themselves as being of Mexican descent [53]. Approximately 27% of the U.S. Hispanic population identify as Puerto Rican, Cuban, Salvadoran, Dominican, Guatemalan, Colombian, Honduran, Ecuadorian, or Peruvian [54].

In 2020, the Hispanic population comprised 18.7% of the U.S. population [51]. As such, they are the largest ethnic minority group in the United States. By 2060, Hispanics are expected to represent 31% of the U.S. population [55]. They are also a young group, with a median age of 29.8 years [51]. In 2019, the three states with the largest Hispanic population growth were Texas (2 million), California (1.5 million), and Florida (1.4 million); these three states have the largest Hispanic populations overall [52].

When involved in the care of Latinx/Hispanic individuals, practitioners should strive to employ *personalismo* (warm, genuine communication) and recognize the importance of *familismo* (the centrality of the family). More flexible scheduling strategies may be more successful with this group, if possible, and some patients may benefit from culturally specific treatment and ethnic and gender matching with providers. Aspects of Latino culture can be assets in treatment: strength, perseverance, flexibility, and an ability to survive.

Native American Patients

The Native American population is extremely diverse. According to the U.S. Census, the terms "Native American," "American Indian," or "Alaskan Native" refer to individuals who identify themselves with tribal attachment to indigenous groups of North and South America [56]. In the United States, there are 574 federally recognized tribal governments and 324 federally recognized reservations [57].

In 2020, it was reported that there were 7.1 million Native Americans in the United States, which is approximately 2% of the U.S. population [57]. By 2060, this number is projected to increase to 10.1 million, or 2.5% of the total population [57].

In general, this group is young, with a median age of 31 years, compared with the general median age of 37.9 years [58]. As of 2018, the states with the greatest number of residents identifying as Native American are Alaska, Oklahoma, New Mexico, South Dakota, and Montana [59]. In 2016, this group had the highest poverty rate (26.2%) of any racial/ethnic group [58].

Listening is an important aspect of rapport building with Native American patients, and practitioners should use active listening and reflective responses. Assessments and histories may include information regarding patients' stories, experiences, dreams, and rituals and their relevance. Interruptions and excessive questioning should be avoided if at all possible. Extended periods of silence may occur, and time should be allowed for patients to adjust and process information. Practitioners should avoid asking about family or personal matters unrelated to presenting issues without first asking permission to inquire about these areas. Native American patients often respond best when they are given suggestions and options rather than directions.

The American Psychological Association recommends that clinicians aim to understand and encourage Indigenous/ethnocultural sources of healing within professional practice.

(https://www.apa.org/about/policy/guidelines-race-ethnicity.pdf. Last accessed September 26, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

White American Patients

In 2021, 76.3% of the U.S. population identified as White alone [60]. The U.S. Census Bureau defines White race as person having origins in any of the original peoples of Europe, the Middle East, or North Africa [38]. While the proportion of population identifying as White only has decreased between 2010 and 2020, the numbers of persons identifying as White and another race/ethnicity increased significantly. The White population in the United States is diverse in its religious, cultural, and social composition. The greatest proportion of this group reports a German ancestry (17%), followed by Irish (13%), English (10%), and Italian (7%) [61].

Providers can assume that most well-accepted treatment approaches and interventions have been tested and evaluated with White American individuals, particularly men. However, approaches may need modification to suit class, ethnic, religious, and other factors.

Providers should establish not only the patient's ethnic background, but also how strongly the person identifies with that background. It is also important to be sensitive to persons multiracial/multiethnic heritage, if present, and how this might affect their family relationships and social experiences. Assumption of White race should be avoided, as White-passing persons of color have their own unique needs.

Multiracial Patients

Racial labels do not always have clear meaning in other parts of the world; how one's race is defined can change according to one's current environment or society. A person viewed as Black in the United States can possibly be viewed as White in Africa. Racial categories also do not easily account for the complexity of multiracial identities. An estimated 3% of United States residents (9 million individuals) indicated in the 2010 Census that they are of more than one race [149]. The percentage of the total United States population who identify as being of mixed race is expected to grow significantly in coming years, and some estimate that it will rise as high as one in five individuals by 2050 [36; 150].

Multiracial individuals often report feeling not fully embraced by any racial or ethnic group, and mistaken identity is a common issue. A small study of multiracial patients assessed their healthcare experiences and noted six commonly encountered microaggressions: mistaken identity, mistaken relationships, fixed forms, entitled examiner, pervasive stereotypes, and intersectionality [144]. It is important to avoid assuming race/culture based only on appearance and to take into account the patient's self-reported identity.

RELIGIOUS, CULTURAL, AND ETHNIC BACKGROUNDS

Religion, culture, beliefs, and ethnic customs can influence how patients understand health concepts, how they take care of their health, and how they make decisions related to their health. Without proper training, clinicians may deliver medical advice without understanding how health beliefs and cultural practices influence the way that advice is received. Asking about patients' religions, cultures, and ethnic customs can help clinicians engage patients so that, together, they can devise treatment plans that are consistent with the patients' values [37].

Respectfully ask patients about their health beliefs and customs and note their responses in their medical records. Address patients' cultural values specifically in the context of their health care. For example, one may ask [37]:

- "Is there anything I should know about your culture, beliefs, or religious practices that would help me take better care of you?"
- "Do you have any dietary restrictions that we should consider as we develop a food plan to help you lose weight?"
- "Your condition is very serious. Some people like to know everything that is going on with their illness, whereas others may want to know what is most important but not necessarily all the details. How much do you want to know? Is there anyone else you would like me to talk to about your condition?"
- "What do you call your illness and what do you think caused it?"
- "Do any traditional healers advise you about your health?"

Practitioners should avoid stereotyping based on religious or cultural background. Each person is an individual and may or may not adhere to certain cultural beliefs or practices common in his or her culture. Asking patients about their beliefs and way of life is the best way to be sure you know how their values may impact their care [37].

The following sections provide a glimpse of the beliefs and practices of the major world religions. This overview is meant only to give a very simple, brief summary of the general ideology of each religion. By no means are all of the rites or beliefs described practiced by all members of each religion; likewise, not all religious rites or beliefs are discussed for each religion. As always, individualized assessment is encouraged.

Judaism

Judaism emerged in the Southern Levant (an area in the Middle East) in about 2000 B.C.E. [136]. There are approximately 13 million Jewish people in the world—6 million in North America, 4.3 million in Asia, and 2.5 million in Europe [137]. Jewish descent is traced through the maternal line, but the choice to practice Judaism is made by the individual. In Jewish tradition, the Torah is believed to be the word of God and the ultimate authority.

There are three tenets of Judaism. The first tenet is monotheism; there is one God who created the universe and continues to rule [138]. The second tenet is that the Jews were chosen to receive the law of God (Yahweh) and to serve as role models for humankind [138]. The third tenet refers to the covenant, which is a contractual agreement between God and the Jewish people. According to the agreement, they will be rewarded if they obey God and keep his commandments; failing to do so would result in divine retribution. Also, they believe that studying the Torah and faithfulness to God and his commandments may hasten the arrival of the Messiah [136; 138].

Jewish law focuses on dietary practices, the Sabbath, and annual holidays or festivals. Observing the dietary laws is called keeping kosher. One's home is considered the table of the Lord, and therefore certain animals considered unclean (e.g., pork, shellfish) are not to be eaten. However, animals with split hooves and animals that chew their cud are acceptable. Acceptable animals must be slaughtered correctly, must have the blood drained from them, and must not be served with dairy products. Those who adhere to kosher laws have separate sets of dishes and utensils for preparing and serving meat, dairy products, and Passover meals [138; 139]. Passover, Hanukkah, Rosh Hashanah, and Yom Kippur are major festivals observed by members of the faith.

Christianity

Christianity emerged in the 1st century C.E. It is the largest religion in North America, and there are approximately 2 billion followers worldwide [136]. There are three major divisions in Christianity: Roman Catholicism, Eastern Orthodoxy, and Protestantism [136; 138]. Christianity is based on the life and teachings of Jesus Christ, and followers believe that salvation

and eternal life can be obtained through their belief in Jesus [137]. The concept of the Trinity is also basic to Christian belief. Although God is perceived as one, God is also expressed in three roles: Father (Creator), Son (Redeemer), and the Holy Spirit (Sustainer) [138; 139].

Baptism and the Eucharist or Holy Communion are the primary sacraments celebrated in most Christian churches [138]. Baptism symbolizes the forgiveness of sins, new life, and initiation into the Christian church. During the baptism, persons are either immersed in water or water is sprinkled or poured over them. Eucharist or Holy Communion is a ritual meal in which bread and wine are taken in remembrance of the body and blood of Jesus that was broken and shed at the cross [136]. Major Christian holidays include Easter (commemorating the death and resurrection of Jesus Christ) and Christmas (celebrating the birth of Jesus).

Christians consider the Bible to be the word of God. It is composed of 66 to 81 separate books (depending on denomination). Christians hold various perspectives on the nature, purpose, and approaches to the interpretation of the Bible.

Islam

Islam is the fastest-growing religion in the United States and throughout the world [140]. Members of Islam are called Muslims, and approximately 3.45 million live in the United States [140]. Islam began in Arabia around 570–632 C.E. and was founded by the prophet Muhammad. It is a monotheistic religion whose followers believe there is one God and that Muhammad was his last Prophet. They believe the Qur'an (or Koran) is the literal word of God (or Allah in Arabic) that was revealed to Muhammad and mediated by Gabriel, the angel of revelation [138]. Arabic is the language used in Islamic prayer/liturgy [137]. Major festivals or holidays include Al-Hijra, Milad un Nabi, Ramadan, Eid al-Fitr, Eid al-Adha, Day of Ashura, and Laylatul Qadr.

Most Muslims are of one of two denominations: Sunni and Shia. While various denominations may have slightly different beliefs or translations, Islam has six major doctrines. The first is the belief in divine unity, or tawhid [136; 138]. The second is the belief in angels as agents of God. Angels have many functions, such as carrying messages to prophets and watching over and keeping track of people. The third is a belief in prophecy as revealed in the Qur'an. The fourth involves belief in scripture (Qur'an), and the fifth is the belief in Judgment Day and life after death [136; 138]. On the Last Day (or final judgment), both the living and the dead will be judged. The faithful will be rewarded, and the unfaithful will be cast into hell. Finally, the sixth doctrine is the Divine Decree and Predestination. It suggests that Allah has already determined who will receive eternal salvation [136; 138].

The Five Pillars are the core beliefs and practices of Islam. The first is the Shahada (profession of faith)—the belief that there is no god but Allah, and Muhammad is his messenger [136]. The second pillar is the Salat (ritual prayer). Muslims pray facing Mecca five times every day: at dawn, noon, mid-afternoon, sunset, and evening [138]. The prayers are usually performed on a rug or mat specifically for this purpose. Zakat (almsgiving) is the third pillar of Islam. Muslims are expected to donate a certain portion of their income to community members in need [138]. Sawm (or fasting) is the fourth pillar of Islam. During the daylight hours of Ramadan, healthy adult Muslims are expected to abstain from food, drink, and sexual relations. This is a time of reflecting, renewing faith, and being grateful for everything Allah has given [138]. The fifth pillar of Islam is Hajj (pilgrimage). After 16 years of age, every Muslim in good health and whose finances permit is expected to visit the holy city of Mecca, located in present-day Saudi Arabia.

Hinduism

Hinduism is one of the world's oldest religions, dating back to about 1500 B.C.E. [138]. Unlike other major religions, it was not founded by a single person but was born of many religious beliefs and philosophies [138]. Hinduism originated in India, and today it is the third-largest religion in the world. There are approximately 1.1 billion adherents worldwide and 2.3 million adherents in the United States [141]. Hinduism is a polytheistic religion with three major deities: Shiva, Vishnu, and Brahma [138]. There are many sacred texts in Hinduism, including The Ramayana, an epic tale of Lord Rama's victory over the 10-headed demon Ravana, and The Mahabharata, the world's longest epic poem that is an historical account of the birth of Hinduism along with a code of ethics for the faithful [136]. Major Hindu festivals include Makar Sankranti, Holi, Diwali, Mahashivratri, Vasant Panchami, Rama Navami, and Janmashtami/Krishna Jayanti.

Two concepts are central to Hinduism: karma and reincarnation. Karma refers to the spiritual principle of cause and effect. In short, people's circumstances are the result of present and past-life actions of good or evil [136]. Hindus also believe in the continuous cycle of life, death, and rebirth (reincarnation) that continues until the soul "transcends all pain and pleasure and release itself from all fears and attachments" [138]. This state is called samsara or transmigration [138].

The Hindu temple is a cultural center where people come to sing, read sacred texts, and perform rituals [136]. The chanting of mantra called pathas is a traditional Hindu practice and is believed to have transformative power. Puja or daily worship is an important aspect of Hinduism. It entails the offering of food, incense, flowers, fruits, ashes, and other articles to an image of a deity [138]. Tirthas refer to pilgrimage sites and holy places in Hinduism [138].

Buddhism

There are approximately 3 million Buddhists in the United States and about 488 million worldwide [141]. Buddhism was founded in northeastern India by Siddhartha Gautam, whose name was later changed to the Buddha or Enlightened One. At 29 years of age, the Buddha sought knowledge from several forest yogis and learned meditation techniques. After six years,

Buddhists believe Gautama found enlightenment while meditating under a Bodhi tree and was released from the cycle of rebirths [138]. He began promoting the idea of a middle path that focused on purity of thought and deed. Buddha believed awareness was the path to overcoming death [136]. He did not want to be worshiped as a god or savior. Instead, he believed his role was to help people find their path to freedom and enlightenment.

The Four Noble Truths and the Eightfold Path are essential to understanding Buddhism. The Four Noble Truths have been identified as the first teaching given by Buddha [137]:

- There is suffering in life.
- Human desire is the cause of suffering.
- The end of human suffering is possible.
- The Eightfold Path is how one achieves nirvana.

Collectively, the Four Noble Truths explain why humans suffer and how to overcome suffering. Within the Four Noble Truths is found the Eightfold Path. Wangu describes the Eightfold Path as consisting of the right opinion, right intentions, right speech, right conduct, right livelihood, right effort, right mindfulness, and right concentration [138]. These eight paths are grouped into three key elements of Buddhist practice: morality, wisdom, and concentration [138].

Buddhists engage in rituals such as chanting and placing flowers, candles, and incense before an image of Buddha. Buddhists celebrate many holidays and festivals, most of which commemorate important events in the life of the Buddha. Every year, Buddhists celebrate Vesak, a festival that commemorates Buddha's birth, enlightenment, and death. During each quarter of the moon, followers of Buddhism participate in a ceremony called Uposatha [136]. This observance allows Buddhists to renew their commitment to their teachings. Buddhist New Year is a time for reflection of past lives and identifying and rectifying mistakes [136].

Confucianism

Confucianism is described as a way of life, philosophy, religion, or ethical code by which to live [138]. It was developed from the teachings of Confucius, who was born around 551 B.C.E. [138]. These teachings focus on good conduct, wisdom, and proper social relationships. Confucius has had a great influence on Chinese culture. Although temples were built to honor him, he is not perceived as a god. The temples are used for public ceremonies only and not as places of worship [138].

Confucianism advocates eight key concepts. The first is Jen, which translates as love, human-heartedness, and goodness [138]. The second concept is Chun-tzu, which refers to a state of centeredness whereby one exhibits Confucians' values effortlessly and without the need for self-monitoring. The third concept is Li, or a sense of order in one's life that coincides with social convention. The fourth concept is Te, or the appropriate use of power by leaders and authority figures. The fifth concept is Wen, which refers to the cultural arts (e.g., music, drama, poetry) that help to maintain unity in society [138]. The remaining concepts are Chi (the wisdom of proper action), Hsin (integrity), and Yi (righteousness or justice).

Taoism

Taoism (pronounced DOW-ism) is a Chinese philosophy and religion dating back to the fourth century B.C.E. [136]. Tao means "the way," and it has no founder or central figures. Taoists do not worship a god. Instead, they focus on coming into harmony with Tao, the cosmic energy that blows through everything. Taoism emphasizes what is natural and going with the flow of life. Today, there are about 20 million Taoists, and most followers live in China, Taiwan, or Southeast Asia [136].

Meditation is an important practice, and the goal of meditation is to come into harmony with the universe [136]. The philosophy is found in a text, the *Tao-te-Ching (Classic Way and Its Power)*, dating back to the third century B.C.E. and attributed to Lao Tzu [138].

Shintoism

Shintoism began during prehistoric times on the Japanese islands [138]. Today, Shinto is the religion of Japan, and it has approximately 112 million followers; more than 75% of them follow Buddhism as well [138]. Like Taoism, Shinto has no founder or central figure. It teaches that all things in the world are imbued with a spirit (kami). Therefore, Shinto followers revere nature in all forms [138].

Most of the deities associated with Shinto are related to nature, such as the sky, earth, heavenly bodies, and storms [136]. However, deities are not different from humans, because everything is imbued with spirit. Everything is connected, including rocks, trees, dust, water, animals, and humans [138].

Shinto has no fixed doctrine and no scripture or sacred text. However, ancient prayers are passed down via oral tradition. Shinto followers worship primarily individually rather than in groups, and followers engage in purification rituals (e.g., handwashing) [138]. Worship occurs outside the shrine, and worshipers usually bring offerings of food or coins for the spirit (*kami*). These offerings are not given as sacrifices but as signs of gratitude [138]. Some followers write prayers on slips of paper and leave them nearby.

New Age Spirituality

The New Age movement became popular in Western society in the 1970s [142]. The precise definition of the term differs among scholars largely due to its highly eclectic range of spiritual beliefs and practices [142; 143]. The movement takes many shapes and is continually changing. However, there are some common features that distinguish it from other religions, such as followers who [136]:

- Look forward to a society that reunites the wisdom of both science and religion

- Adopt holistic and alternative healing methods
- Embrace a wide array of traditional and nontraditional spiritual beliefs and practices
- Accept the existence of a universal energy that undergirds and permeates all of existence

Adherents believe healing can occur when individuals connect with this universal energy and learn to use it. This energy has been called by many names by different cultures, including *chi* (Chinese), *ki* (Japanese), *prana* (Sanskrit), *mana* (Pacific Islander), or the use of self as a final authority [136].

GENDER

Gender identity is a vital aspect of a person's experience of the world and of themselves. It also impacts the ways in which the world perceives and treats individuals, with a clear effect on the effective provision of health and mental health care. This section will focus on persons presenting as cisgender male or female; special considerations for those who are transgender, non-binary, or gender nonconforming will be explored in the next section.

An increasing amount of research is supporting a relationship between men's risk for disease and death and male gender identity, and the traditional male role has been shown to conflict with the fostering of healthy behaviors [62; 63]. Male gender identity is related to a tendency to take risks, and the predilection for risky behavior begins in boyhood [63; 64; 65]. In addition, boys are taught that they should be self-reliant and independent and should control their emotions, and societal norms for both boys and men dictate that they maintain a strong image by denying pain and weakness [62; 64; 65].

Issues related to male gender identity have several important implications for health. First, risky behavior is associated with increased morbidity and mortality. Second, the concept of masculinity leads to inadequate help- and information-seeking behavior and a reduced likelihood to engage in behavior to promote health [62; 64; 65]. These behaviors appear to be rooted in a decreased likelihood for men to perceive themselves as being ill or at risk for illness, injury, or death [62]. Third, male gender identity, coupled with lower rates of health literacy, creates special challenges for effectively communicating health messages to men [66; 67; 68]. Gender differences in health-related behaviors are consistent across racial/ethnic populations, although specific behaviors vary according to race/ethnicity [63].

Men's beliefs about masculinity and traditional male roles affect health communication, and healthcare practitioners should consider male-specific beliefs and perceptions when communicating with male patients. For example, because men tend to focus on present rather than future health, concepts of fear, wellness, and longevity often do not work well in health messages [69]. Instead, healthcare practitioners should focus more on "masculine" concepts, such as strength, safety, and performance, all of which tie into men's perceptions of their roles as providers and protectors.

Although men are more likely than women to lack a regular healthcare provider and to avoid seeking help or information, women are more likely to have a chronic condition requiring regular monitoring and are more likely to have forgone necessary health care due to the cost [70]. In general, women are disproportionately affected by stresses related to caregiving, and this can be a barrier to help-seeking. Caregiving has been socialized as a feminine role, and two out of every three caregivers in the United States are women, meaning they provide daily or regular support to children, adults, or people with chronic illnesses or disabilities [145]. Women who are caregivers have a greater risk for poor physical and mental health, including depression and anxiety.

Women are more likely than men to be diagnosed with a mental health disorder, and more than 20% of women in the United States experienced a mental health condition in the past year [146]. In addition to being disproportionately affected, mental health conditions, such as depression and bipolar disorder, can manifest differently in or have different impacts on women than men. Much of the research into women's health has focused on the perinatal period, which limits our knowledge of how mental illness affects women's lives.

There is also some evidence that women's pain is less likely to be taken seriously and controlled than male patients. A series of four studies found a relative gender-pain exaggeration bias, wherein perceivers believe women, relative to men, to be emotionally dramatizing and therefore more likely to exaggerate versus downplay their pain [147]. This bias may lead perceivers to interpret women's, relative to men's, pain reports as overstatements, inauthentic, or dramatized.

Providing gender-sensitive care to women involves overcoming the limitations imposed by the dominant medical model in women's health. This requires theoretical bases that do not reduce women's health and illness experience into a disease. This philosophy incorporates explanations of health and empowers women to effectively and adequately deal with their situations. The major components incorporated into the development of sensitive care include:

- Gender is a central feature.
- Women's own voices and experiences are reflected.
- Diversities and complexities are incorporated into women's experiences.
- Theorists reflect about underlying androcentric and ethnocentric assumptions.
- Sociopolitical contexts and constraints of women's experiences are considered.
- Guidelines for practice with specific groups of women are provided.

GENDER AND SEXUAL MINORITIES

The gender and sexual minority (GSM) population is a diverse group that can be defined as a subculture. It includes homosexual men, lesbian women, bisexual persons, transgender individuals, and those questioning their sexual identity, among others. The GSM population is diverse, representing all ages and all socioeconomic, ethnic, educational, and religious backgrounds. The population has been described as "hidden and invisible," "marginalized," and "stigmatized." As a result, the unique health and safety needs of the population have often been overlooked or ignored. Clear definitions of the concepts related to sexual identity will be helpful. The following is a glossary of terms used in discussions of this group [71; 72; 73; 74; 75; 76]:

Asexual/aromantic: An individual who does not experience sexual attraction. There is considerable diversity in individuals' desire (or lack thereof) for romantic or other relationships.

Bisexual: An adjective that refers to people who relate sexually and affectionately to both women and men.

Coming-out process: A process by which an individual, in the face of societal stigma, moves from denial to acknowledging his/her sexual orientation. Successful resolution leads to self-acceptance. Coming out is a lifelong process for lesbian, gay, bisexual, and transgender persons and their families and friends as they begin to tell others at work, in school, at church, and in their communities.

Gay: The umbrella term for GSM persons, although it most specifically refers to men who are attracted to and love men. It is equally acceptable and more accurate to refer to gay women as "lesbians."

Gender and sexual minorities (GSM): A term meant to encompass lesbian, gay, bisexual, trans, queer/questioning, intersex/intergender, asexual/ally (LGBTQIA) people as well as less well-recognized groups, including aromantic, two-spirited, and gender-fluid persons.

Heterosexism: An institutional and societal reinforcement of heterosexuality as the privileged and powerful norm.

Heterosexuality: Erotic feelings, attitudes, values, attraction, arousal, and/or physical contact with partners of the opposite gender.

Homophobia: A negative attitude or fear of non-straight sexuality or GSM individuals. This may be internalized in the form of negative feelings toward oneself and self-hatred. Called "internalized homophobia," it may be manifested by fear of discovery, denial, or discomfort with being LGBTQIA, low self-esteem, or aggression against other lesbians and gay men.

Homosexuality: The "persistent sexual and emotional attraction to members of one's own gender" as part of the continuum of sexual expression. Typically not used to describe people.

LGBTQIA: An acronym used to refer to the lesbian, gay, bisexual, transgender/transsexual, queer/questioning, intersex/intergender, asexual/ally community. In some cases, the acronym may be shortened for ease of use or lengthened for inclusivity. Members of this group may also be referred to as gender and sexual minorities (GSM).

Queer: An umbrella term to describe persons with a spectrum of identities and orientations that are outside of the heteronormative standard.

Sexual identity: The inner sense of oneself as a sexual being, including how one identifies in terms of gender and sexual orientation.

Sexual orientation: An enduring emotional, romantic, sexual, and/or affectionate attraction to another person. Individuals may experience this attraction to someone of the same gender, the opposite gender, both genders, or gender nonconforming.

Transgender: An umbrella term describing a number of distinct gender positions and identities including: crossdressing, transsexual, nonbinary, and intersex.

One's intrapersonal acceptance or rejection of societal stereotypes and prejudices, the acceptance of one's self-identity as a sexual minority, and how much one affiliates with other members of the GSM community varies greatly among individuals [77]. Some authors stress the diversity within the GSM community by discussing "GSM populations" [78]. For example, it is understandable that a GSM population living in rural areas of the United States would have little in common with a GSM population living in urban areas or "gay-friendly" neighborhoods. Additionally, mental health experts have suggested that "GSM community" symbolizes a single group of individuals who express their sexuality differently than the majority of heterosexual individuals. However, many distinct communities have been identified, including lesbian, gay, bisexual, and transgender [79]. Each community is different from the other as well as different from the heterosexual community. A culturally competent healthcare provider should keep this diversity in mind so that vital differences among these smaller groups are not lost when thinking of the GSM population in general.

Commonalities exist among the GSM communities as well. For example, many adolescents, whether gay, lesbian, bisexual, transgender, or questioning their sexual identity, lack sexual minority role models to assist with successful psychosocial development [79].

The subtle and pervasive ways that discomfort with GSM individuals may be manifested have been examined and, in some instances, categorized as "cultural heterosexism," which is characterized by the stigmatization in thinking and actions found in our nation's cultural institutions, such as the educational and legal systems [80]. "Cultural heterosexism fosters individual antigay attitudes by providing a ready-made system of values and stereotypical beliefs that justify such prejudice as natural" [81]. Perhaps the paucity of information about the

GSM community in basic professional education has been a reflection of cultural heterosexism. Writers, funding sources, and publishers have been exposed to the same cultural institutions for many years.

Individuals generally begin to absorb these institutional attitudes as children and may consequently develop "psychologic heterosexism," which may also manifest as antigay prejudice. Many individuals, as children, have little contact with someone who is openly gay and, as a result, may not be able to associate homosexuality with an actual person. Instead, they may associate it with concepts such as "sin," "sickness," "predator," "outsider," or some other negative characteristic from which the individual wants to maintain distance [81]. Psychologic heterosexism involves (among other factors) considering sexual identity and determining that one does not want to think further about it. The direction of this thinking is undeniably negative, resulting in an environment that allows antigay hostility [81]. The impact of antigay prejudice on the physical and mental health of members of the LGBTQIA community and their families should not be underestimated [82; 83].

Sexual minority individuals also are not immune to societal attitudes and may internalize negative aspects of the antigay prejudice experience. Anxiety, depression, social withdrawal, and other reactions may result [2; 84]. While the study of psychologic heterosexism, both blatant and subtle, is in the early stages of research, it has had a measurable impact on the mental health of the GSM community [85; 86; 87; 88].

Examples of the range of manifestations of heterosexism and/or homophobia in our society are readily available. Without difficulty, each example presented here may be conceptualized as related to the emotional or physical health of a GSM individual or family member:

- A kindergarten student calls another child an LGBTQ+ slur but does not really know what he is saying.
- A teenage girl allows herself to become pregnant, "proving" her heterosexuality to herself, her family, and her friends.
- A parent worries that her 12-year-old daughter is still a "tomboy."
- An office employee decides to place a photo of an old boyfriend in her office rather than a photo of her gender-nonconforming partner of five years.
- A college student buries himself in his studies in an effort to ignore his same-sex feelings and replace feelings of isolation.
- Two teenage girls, thought by peers to be transgender individuals, are assaulted and killed while sitting together in an automobile.
- A female patient is told by a healthcare provider that her haircut makes her look like a lesbian and is examined roughly.
- A gay man chooses not to reveal his sexual identity to his healthcare provider out of fear of a reduction or withdrawal of healthcare services.

The manifestations of heterosexism have inhibited our learning about the LGBTQIA population and its needs [78]. Gay patients have feared open discussion about their health needs because of potential negative reactions to their self-disclosure. Prejudice has impacted research efforts by limiting available funding [77]. All of these factors emphasize that the healthcare education system has failed to educate providers and researchers about the unique aspects of LGBTQIA health [83; 89].

Common Myths

Many myths surround homosexuality; a few are outlined below. The origin of these myths may be better understood after examining the history of homosexuality as well as the attitudes toward human sexuality in general. The history of the development of societal norms related to homosexuality includes misconceptions developed during times when research was not available on which to build a scientific knowledge base [82; 90; 91; 92].

Myth: Sexual orientation is a choice.

Fact: No consensus exists among scientists about the reasons that an individual develops his/her sexual orientation. Some research has shown that the bodies and brains of gay men and women differ subtly in structure and function from their heterosexual counterparts; however, no findings have conclusively shown that sexual orientation is determined by any particular factor or set of factors. Many people confuse sexual orientation with sexual identity. The reader may consider reviewing the definitions of these terms when further considering this myth.

Myth: Gay men and lesbians can be easily identified because they have distinctive characteristics.

Fact: Most gay and lesbian individuals conform to the majority of society in the way they dress and act. Further, a person's appearance is not necessarily an indication of sexual or romantic interests.

Myth: Gay individuals are child molesters.

Fact: This is a very damaging and heterosexist position. According to experts in the field of sexual abuse, the vast majority of those who molest children are heterosexual. The average offender is a White heterosexual man whom the child knows.

Myth: Gay people want to come into our schools and recruit our children to their "lifestyle."

Fact: Efforts to bring issues related to LGBTQIA history and rights into schools are not efforts to "convert," just as education on European history is not an effort to glamorize or "convert" to European identity. The intent has been to teach a more complete history of the world and to prevent children from mistreating LGBTQIA individuals, who are often the subjects of harassment and physical attacks. There is no evidence that people could be "recruited" to a gay sexual orientation, even if someone wanted to do this.

AGE

Elderly patients should be routinely screened for health and mental health conditions using tools specifically developed for this population, in spite of some practitioners' discomfort with asking questions about sensitive topics. These population-appropriate assessments may be included in other health screening tools [93].

Wellness and purpose have become important emphases when working with older adults [94]. In the past, aging was associated with disability, loss, decline, and a separation from occupational productivity. Although patient growth and positive change and development are values that practitioners embrace, the unconscious acceptance of societal myths and stereotypes of aging may prevent practitioners from promoting these values in elderly individuals [95].

Common Myths of Aging

Society holds several myths about the elderly. Many of these myths may be easily disputed based on data from the U.S. Census and other studies.

Myth: Most older adults live alone and are isolated.

Fact: In 2018, 70% of men and 46% of women 65 years and older were married. An estimated 28% lived alone [96]. According to a survey conducted in 2009, 9 out of 10 individuals 65 years of age and older stated they talked to family and friends on a daily basis [97]. In 2016, an estimated 20% of the U.S. population lived in a household comprised of two adult generations or a grandparent or at least one other generation, compared with 12% in 1980 [97; 98]. This multigenerational household trend particularly affects those 65 years and older, with 21% of these individuals living in multigenerational households in 2016. This group was second only to individuals 25 to 29 years of age (33%) [98]. Several factors have contributed to this trend, including growing racial and ethnic diversity and adults getting married later [97; 98].

Myth: Most older adults engage in very minimal productive activity.

Fact: In 2016, 18.6% of persons 65 years and older were employed or actively looking for work, and this population represents approximately 8% of the total labor force in the United States [99]. The elderly are more engaged in self-employed activities than younger persons. In 2016, 16.4% of those 65 years of age and older were self-employed, compared with an average of 5.5% of those 16 years to 64 years of age [100].

Myth: Life satisfaction is low among the elderly.

Fact: Data from the Berkeley Older Generation Study indicate that many elders are quite satisfied with their life [101]. More than one-third (36%) of persons older than 59 years of age and 15% of those older than 79 years of age stated they were currently experiencing the best time in their lives. A 2009 survey found that 60% of individuals 65 years of age and older stated they were very happy. A 2012 survey found that 65% of individuals 65 years of age and older indicated that the past year of their life has been normal or better than normal, and more than 80% of respondents agreed with the statement, "I have a strong sense of purpose and passion about my life and my future" [102]. Most of the factors that predict happiness for the young, such as good health and financial stability, also apply to the elderly. Older adults tend to report higher levels of well-being in part due to the quality of their social relationships [103].

PERSONS WITH MENTAL OR PHYSICAL DISABILITY

Americans with disabilities represent a large and heterogeneous segment of the population. The prevalence of disability varies by age group and definition. Based on the U.S. Census Bureau's 2013 American Community Survey (ACS), which describes disability in terms of functional limitations, 12.6% of the civilian U.S. noninstitutionalized population has a disability, defined as difficulty in hearing or vision, cognitive function, ambulation, self-care, or independent living [104]. The U.S. Department of Education, which uses categorical disability labels, estimates that 13% of children and youth 3 to 21 years of age have a disability (defined as specific learning disabilities, speech or language impairments, intellectual disability, emotional disturbance, hearing impairments, orthopedic impairments, other health impairments, visual impairments, multiple disabilities, deaf-blindness, autism, traumatic brain injury, or developmental delay) [104].

People with disabilities experience many health disparities. Some documented disparities include poorer self-rated health; higher rates of obesity, smoking, and inactivity; fewer cancer screenings (particularly mammography and Pap tests); fewer breast-conserving surgeries when breast cancer is diagnosed; and higher rates of death from breast or lung cancer [104].

Disability cultural competence requires appreciation of social model precepts, which recognize patients' rights to seek care that meets their expectations and values. The social model of disability has been characterized as centering disability as a social creation rather than an attribute of the patient [105]. As such, disability requires a social/political response in order to improve environmental factors affecting access and acceptance [105]. This involves adoption of person-first language, acknowledgement of social and environmental factors impacting persons abilities, and confronting disability-associated stigma.

VETERANS

The effects of military service and deployment to military combat on the individual and the family system are wide-reaching. According to the U.S. Department of Defense, there were 3.5 million current military personnel in 2020 and 18.3 million veterans in 2017 [132; 133]. The Army has the largest number of active duty members, followed by the Navy, the Air Force, and the Marine Corps [132]. Military service presents its own set of risk and protective factors for a variety of mental health issues, including post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), depression and suicide, substance

abuse, and interpersonal violence. In particular, transitioning from combat back to home life can be particularly trying for veterans and their families.

As the number of military conflicts and deployments has increased since 2001, the need to identify and provide better treatment to veterans and their families has become a greater priority. The first step in providing optimal care is the identification of veterans and veteran families during initial assessments, with an acknowledgement that veterans may be any sex/gender and are present in all adult age groups [133].

Unfortunately, veterans and military families often do not voluntarily report their military service in healthcare appointments. In 2015, the American Medical Association updated its recommendations for social history taking to include military history and veteran status [134]. In addition, the American Academy of Nursing has designed the Have You Ever Served? Initiative to encourage health and mental health professionals to ask their patients about military service and related areas of concern [135]. This program provides pocket cards, posters, and resource links for professionals working with veterans and their families. Recommended questions for intake include [135]:

- Have you or has someone close to you ever served in the military?
- When did you serve?
- Which branch?
- What did you do while you were in the military?
- Were you assigned to a hostile or combative area?
- Did you experience enemy fire, see combat, or witness casualties?
- Were you wounded, injured, or hospitalized?
- Did you participate in any experimental projects or tests?
- Were you exposed to noise, chemicals, gases, demolition of munitions, pesticides, or other hazardous substances?

DIETARY CONSIDERATIONS

Cultural or personal beliefs can also impact the dietary needs of patients, which, in turn, can affect their health and adherence to prescribed treatments. For example, health issues related to fasting may arise among Buddhists, Hindus, Muslims, and some Christian patients, as well as persons of other faiths. This may particularly become an issue during extended fasts, such as the Muslim observance of Ramadan, which continues for one month [148]. Fasting is done during Ramadan as a spiritual exercise and is mandatory for all healthy adults. Those exempt from Ramadan fasting include children (prior to the onset of puberty); developmentally disabled individuals; the elderly; those who are acutely or chronically ill, for whom fasting would be detrimental to health; travelers who have journeyed more than approximately 50 miles; and pregnant, menstruating, or breastfeeding women [148]. Practitioners should advise all patients for whom fasting would prevent healing or adequate care (e.g., inability to take medication) to postpone or abstain from the ritual, if possible [148].

Another dietary consideration for some patients is whether medications contain animal-sourced ingredients. Vegetarians, vegans, Jewish people, Muslims, and others may need to know which products are from animal sources. Common examples of meds that contain ingredients from animals include:

- Desiccated thyroid from pig thyroid glands
- Heparin from pig intestines
- Pancreatic enzymes from pig pancreases
- Certain vaccines grown in eggs
- Conjugated estrogens from pregnant mares' urine

In addition, the gelatin used to make capsules and even some tablets and vaccines is often hydrolyzed collagen from animal tissues. Over-the-counter medications and supplements that may have animal-source ingredients include glucosamine (from shellfish), vitamin D3 (from lanolin, or sheep's wool), calcium (from oyster shells or bone meal), and omega-3 fatty acids (from fish oils).

PROMOTING CULTURALLY SENSITIVE COMMUNICATION

Communication, the process of sending a message from one party to another, consists of both verbal and nonverbal components. Verbal and nonverbal communications are embedded within the culture of the parties disseminating the information and within the culture of the parties receiving the information. Communication is complex and multilayered because it involves unstated, implicit rules about a variety of factors, including physical distance between parties, tone of voice, acceptable topics of discussion, physical contact, and amount of eye contact [106]. Each of these variables is influenced by the perception of the level of formality/informality of the situation. Frequently, misunderstandings occur because the decoding and interpretation of these nonverbal cues are not accurate.

The verbal component of communication is just as complicated. Certainly, similarity in language shared by both parties enhances communication, but assuming that both parties in a conversation speak the same language, how the information is interpreted is still influenced by a host of factors. Linguists have posited that approximately 14,000 different meanings and interpretations can be extracted from the 500 most common English words [107]. Consequently, practitioners must be aware of the different communication styles held by diverse ethnic minority patients, as the clinical communication process is the primary vehicle by which problems and solutions are identified and conveyed [108].

Styles of communication can be classified from high- to low-context [109]. High-context cultures are those cultures that disseminate information relying on shared experience, implicit messages, nonverbal cues, and the relationship between the two parties [107; 110]. Members of these cultural groups tend to listen with their eyes and focus on how something was said or conveyed [106; 109]. On the other hand, low-context cultures rely on verbal communication or what is explicitly stated in the conversation [107]. Consequently, low-context communicators listen with their ears and focus on what is being said [106; 109; 110]. Western culture, including the United States, can be classified as a low-context culture. On the other hand, groups from collectivistic cultures, such as Asian/Pacific Islanders, Hispanics, Native Americans, and African Americans, are from high-context cultures [109].

Communicators from high-context cultures generally display the following characteristics [106; 107; 110; 111]:

- Use of indirect modes of communication
- Use of vague descriptions
- Less talk and less eye contact
- Interpersonal sensitivity
- Use of feelings to facilitate behavior
- Assumed recollection of shared experiences
- Reliance on nonverbal cues such as gestures, tone of voice, posture, voice level, rhythm of speaking, emotions, and pace and timing of speech
- Assimilation of the "whole" picture, including visual and auditory cues
- Emotional speech
- Use of silence
- Use of more formal language, emphasizing hierarchy between parties

On the other hand, low-context communicators can typically be described as [106; 107; 110]:

- Employing direct patterns of communication
- Using explicit descriptions and terms
- Assuming meanings are described explicitly
- Utilizing and relying minimally on nonverbal cues
- Speaking more and often raising their voices (more animated, dramatic)
- Often being impatient to get to the point of the discussion
- Using more informal language; less emphasis on hierarchy, more equality between parties (more friendly)
- Being more comfortable with fluidness and change
- Uncomfortable using long pauses and storytelling as a means of communicating

Understanding the distinctions between individuals who come from high- and low-context cultures can promote cultural sensitivity. However, it is vital that practitioners take heed of several words of caution. First, it is important not to assume that two individuals sharing the same culture (e.g., low-context culture) will automatically have a shared script for communicating. Second, it is important to not immediately classify an individual into a low- or high-context culture because of their ethnicity. A Chinese American man may not necessarily be a high-context communicator because he is Asian. A host of factors, such as level of acculturation, upbringing and socialization, education, and family immigration history, will all play a role in how one learns to communicate. Third, a major criticism of the discussion of low-/high-context cultures is that they reinforce dualism and ultimately oversimplify the complexities and nuances of communication [112].

Learning to communicate effectively also requires an understanding of how different conversational traits influence the communication process, or how information is conveyed and interpreted. Again, the goal of this section is not to simply dichotomize individuals' conversational styles into categories, but rather to understand the factors that play a role in how someone makes a decision on how to communicate [106].

As long as there are two parties involved in a conversation, nonverbal communication is inevitable, and it becomes salient particularly when it is processed from one culture to another. Nonverbal communication is any behavior (including gestures, posture, eye contact, facial expressions, and body positions) that transcends verbal or written forms of communication [113]. Nonverbal communication can enhance or reinforce what is said verbally, and conversely, it can completely contradict the message communicated verbally. It can also end up replacing what was verbally communicated if both parties do not share a native language [114].

In Western culture, communication is more direct and eye contact is highly valued. When eye contact is not maintained, many Westerners assume that the party is hiding pertinent information. However, in some cultures, reducing eye contact is a sign of respect [108]. Conversely, patients may interpret direct and indirect gazes differently. For example, in one study, Japanese individuals tended to rate faces with a direct gaze as angry and less pleasant compared with Finnish participants [115].

The amount of social space or distance between two communicating parties is culturally charged as well. Depending upon the social context, Westerners tend to maintain a distance of about three feet, or an arm's length, in conversations [107]. In a public setting, where both parties are engaged in a neutral, nonpersonal topic, Westerners will feel encroached upon and uncomfortable if an individual maintains a closer conversational distance. However, in other cultures, such as Latino and Middle Eastern, a closer distance would be the norm [107]. Chung recommends that in a clinical setting the practitioner allow patients to set the tone and social distance

[116]. The practitioner can sit first and permit the patient to select where they want to sit.

Cross-cultural communication is by no means simple, and there is no set of rules to merely abide by. Instead, promoting culturally sensitive communication is an art that requires practitioners to self-reflect, be self-aware, and be willing to learn. Therefore, as practitioners become skilled in noticing nonverbal behaviors and how they relate to their own behaviors and emotions, they will be more able to understand their own level of discomfort and comprehend behavior from a cultural perspective [106].

CULTURALLY SENSITIVE ASSESSMENT GUIDELINES

Practitioners may be categorized as either disease-centric or patient-centric [117]. Disease-centered practitioners are concerned with sign/symptom observation and, ultimately, diagnosis. On the other hand, patient-centered practitioners focus more on the patient's experience of the illness, subjective descriptions, and personal beliefs [117]. Patient-centered practice involves culturally sensitive assessment. It allows practitioners to move assessment and practice away from a pathology-oriented model and instead acknowledge the complex transactions of the individual's movement within, among, and between various systems [118].

Practitioners who engage in culturally sensitive assessment nonjudgementally obtain information related to the patient's cultural beliefs, overall perspective, and specific health beliefs [119]. They also allow the patient to control the timing [120].

The goal is to avoid the tendency to misinterpret health concerns of ethnic minority patients. Panos and Panos have developed a qualitative culturally sensitive assessment process that focuses on several domains [119]. Each domain includes several questions a practitioner may address in order to ensure that he or she is providing culturally responsive care.

Alternatively, Kleinman suggests that the practitioner ask the patient what he or she thinks is the nature of the problem [121]. He highlights the following types of questions that may be posed to the patient [121]:

- Why has the illness/problem affected you?
- Why has the illness had its onset now?
- What course do you think the illness will follow?
- How does the illness affect you?
- What do you think is the best or appropriate treatment? What treatment do you want?
- What do you fear most about the illness and its treatment?

Similar to Kleinman's culturally sensitive assessment questions, Galanti has proposed the 4 Cs of Culture [122]:

- What do you call the problem?
- What do you think caused it?
- How do you cope with the problem?
- What questions or concerns do you have about the problem or treatment?

Pachter proposed a dynamic model that involves several tiers and transactions, similar to Panos and Panos' model [123]. The first component of Pachter's model calls for the practitioner to take responsibility for cultural awareness and knowledge. The professional must be willing to acknowledge that they do not possess enough or adequate knowledge in health beliefs and practices among the different ethnic and cultural groups they come in contact with. Reading and becoming familiar with medical anthropology is a good first step.

The second component emphasizes the need for specifically tailored assessment [123]. Pachter advocates the notion that there is tremendous diversity within groups. Often, there are many intersecting variables, such as level of acculturation, age at immigration, educational level, and socioeconomic status, that influence health ideologies. Finally, the third component involves a negotiation process between the patient and the professional [123]. The negotiation consists of a dialogue that involves a genuine respect of beliefs. The professional might recommend a combination of alternative and Western treatments.

Beckerman and Corbett further recommend that recently immigrated families be assessed for [124]:

- Coping and adaptation strengths
- Issues of loss and adaptation
- The structure of the family in terms of boundaries and hierarchies after immigration
- Specific emotional needs
- Acculturative stress and conflict for each family member

Practitioners should seek to understand the sociopolitical context of the origin country [125]. A migration narrative is also recommended, whereby an individual provides a story of their migration history. Asking about how long the family has been in the United States, who immigrated first, who was left behind, and what support networks are lacking gives the practitioner an overview of the individual's present situation [126]. The theme of loss is very important to explore. Types of losses may include family and friends left behind, social status, social identity, financial resources, and familiarity [126]. For refugees and newly immigrated individuals and families, assessment of basic needs (e.g., food, housing, transportation) is necessary [125].

Culturally sensitive assessment involves a dynamic framework whereby the practitioner engages in a continual process of questioning. Practitioners should work to recognize that there are a host of factors that contribute to patients' multiple identities (e.g., race, gender, socioeconomic status, religion) [127].

CREATING A WELCOMING AND SAFE ENVIRONMENT

Improving access to care can be facilitated, in part, by providing a welcoming environment. The basis of establishing a safe and welcoming environment for all patients is security, which begins with inclusive practice and good clinician-patient rapport. Shared respect is critical to a patient's feeling of psychological well-being. Security can also be fostered by a positive and safe physical setting. For patients who are acutely ill, both the illness experience and treatment process can produce trauma. This is particularly true if involuntary detainment or hospitalization is necessary, but exposure to other individuals' narratives of experienced trauma or observing atypical behaviors from individuals presenting as violent, disorganized, or harmful to themselves can also be traumatic. As such, care environments should be controlled in a way to minimize traumatic stress responses. Providers should keep this in mind when structuring the environment (e.g., lighting, arrangement of space), creating processes (e.g., layout of appointments or care systems, forms), and providing staff guidance (e.g., nonverbal communication, intonation, communication patterns). During each encounter, the patient's perception of safety is impacted by caretakers and ancillary staff.

Experts recommend the adoption and posting of a nondiscrimination policy that signals to both healthcare providers and patients that all persons will be treated with dignity and respect [128]. Also, checklists and records should include options for the patient defining their race/ethnicity, preferred language, gender expression, and pronouns; this can help to better capture information about patients and be a sign of acceptance to that person. If appropriate, providers should admit their lack of experience with patient subgroups and seek guidance from patients regarding their expectations of the visit.

Front office staff should avoid discriminatory language and behaviors. For example, staff should avoid using gender-based pronouns, both on the phone and in person. Instead of asking, "How may I help you, sir?" the staff person could simply ask, "How may I help you?" Offices that utilize electronic health records should have a system to track and record the gender, name, and pronoun of all patients. This can be accomplished by standardizing the notes field to document a preferred name and pronoun for all patients [129]. Some persons who identify as non-binary (i.e., neither or both genders) may prefer that plural pronouns (e.g., they) be used.

Questions should be framed in ways that do not make assumptions about a patient's culture, gender identity, sexual orientation, or behavior. Language should be inclusive, allowing the patient to decide when and what to disclose. Assurance of confidentiality should be stressed to the patient to allow for a more open discussion, and confidentiality should be ensured if a patient is being referred to a different healthcare provider. Asking open-ended questions can be helpful during a history and physical.

The FACT acronym may be helpful for healthcare providers. Providers should:

- Focus on those health issues for which the individual seeks care
- Avoid intrusive behavior
- Consider people as individuals
- Treat individuals according to their gender

Training office staff to increase their knowledge and sensitivity toward persons will also help facilitate a positive experience for patients.

CONCLUSION

Culture serves as a lens through which patients and practitioners filter their experiences and perceptions. Patients will bring their unique life stories and concerns to the practitioner, and their cultural values and belief systems will inevitably shape how the problem is defined and their beliefs about what is effective in solving the problem. However, the cultural backgrounds and values of patients are not necessarily scripts that define behavior, and when practitioners view culture as a strength and not a pathology, practitioners will be able to more effectively join with patients to mobilize change.

Customer Information/Answer Sheet/Evaluation insert located between pages 60–61.

TEST QUESTIONS
#97510 INTERCULTURAL COMPETENCE AND PATIENT-CENTERED CARE

This is an open book test. Please record your responses on the Answer Sheet.
A passing grade of at least 80% must be achieved in order to receive credit for this course.

This 4 Credit activity must be completed by September 30, 2026.

1. A nurse acknowledges that she still has a lot to learn about different racial and ethnic minority groups. She is willing to learn from her patients and assume the role of learner. This nurse is demonstrating
- A) *diversity.*
- B) *reflexivity.*
- C) *explicit bias.*
- D) *cultural humility.*

2. Intersectionality is a term to describe the multiple facets of identity, including race, gender, sexual orientation, religion, sex, and age.
- A) *True*
- B) *False*

3. An alternative way of conceptualizing implicit bias is that an unconscious evaluation is only negative if it has further adverse consequences on a group that is already disadvantaged or produces inequities.
- A) *True*
- B) *False*

4. Which of the following is NOT a risk factor in triggering implicit biases for health professionals?
- A) *Uncertainty*
- B) *Cognitive dissonance*
- C) *Time pressure to make a rapid decision*
- D) *Heavy workload and feeling behind schedule*

5. All of the following are categories of social determinants, EXCEPT:
- A) *Race*
- B) *Economic stability*
- C) *Health care access and quality*
- D) *Social and community context*

6. Which of the following has been identified as a core value of Black culture?
- A) *Spirituality*
- B) *Community*
- C) *Family/kinship*
- D) *All of the above*

7. Native American patients often respond best when they are given directions rather than suggestions and options.
- A) *True*
- B) *False*

8. Male gender identity is related to
- A) *risk avoidance.*
- B) *emotional demonstration.*
- C) *denying pain and weakness.*
- D) *teamwork and help-seeking.*

9. Cultural heterosexism is characterized by
- A) *negative feelings toward oneself and self-hatred.*
- B) *A negative attitude or fear of non-straight sexuality or GSM individuals.*
- C) *considering sexual identity and determining that one does not want to think further about it.*
- D) *the stigmatization in thinking and actions found in cultural institutions, such as educational and legal systems.*

10. Persons with disability experience higher rates of all of the following, EXCEPT:
- A) *Obesity*
- B) *Smoking*
- C) *Cancer screening*
- D) *Breast and lung cancer mortality*

Test questions continue on next page ➞

11. Low-context cultures rely on verbal communication or what is explicitly stated in the conversation.
- A) *True*
- B) *False*

12. Which of the following is a typical characteristic of communication in high-context cultures?
- A) *Use of more informal language*
- B) *Speaking more and often raising one's voice*
- C) *Assumption that meanings are described explicitly*
- D) *Reliance on interpreting eye contact, gestures, and tone of voice*

13. Which of the following is an attribute of patient-centered practice?
- A) *The practitioner focuses on observed signs and symptoms.*
- B) *The practitioner is concerned with identifying the disease pathology.*
- C) *The practitioner focuses on the subjective description of the illness.*
- D) *The practitioner is not influenced by how the client/patient defines the illness.*

14. The basis of establishing a safe and welcoming environment for all patients is
- A) *security.*
- B) *autonomy.*
- C) *beneficence.*
- D) *maintaining distance.*

15. It is never appropriate for providers to admit their lack of experience with patient subgroups or to seek guidance from patients.
- A) *True*
- B) *False*

Be sure to transfer your answers to the Answer Sheet located on the envelope insert.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Substance Use Disorders and Pain Management: MATE Act Training

This course meets the Pennsylvania requirement for pain managment, addiction, and opioid education, and meets 8 hours of patient safety/risk management education.

This course meets the Federal MATE Act requirement for 8 hours of training for physicians and physician assistants with a new or renewing DEA license. This course may be completed for general CE.

In addition to receiving *AMA PRA Category 1 Credit™*, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board: 8 ABIM MOC Points, 8 ABS Points, 8 ABA MOC Points, 8 ABP MOC Points, 8 ABPath Points.

Audience

This course is designed for all healthcare professionals who may alter prescribing practices or intervene to help meet the needs of patients with substance use disorders.

Course Objective

The purpose of this course is to provide clinicians who prescribe or distribute controlled substances with an appreciation for the complexities of managing patients with substance use disorders and comorbid pain in order to provide the best possible patient care and to prevent a growing social problem.

Learning Objectives

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

1. Outline substance use disorder risk factors, screening, and diagnosis.
2. Describe the role of psychosocial therapies in the management of substance use disorders.
3. Compare and contrast available pharmacotherapeutic options for the treatment of alcohol, tobacco, and opioid use disorders.
4. Discuss the impact of polysubstance use and co-occurring mental disorders and substance use disorder presentation and treatment.
5. Review legal and ethical issues related to substance use disorder treatment.
6. Create comprehensive treatment plans for patients with pain that address patient needs as well as drug diversion prevention.
7. Evaluate behaviors that may indicate drug seeking or diverting as well as approaches for patients suspected of misusing opioids.
8. Identify state and federal laws governing the proper prescription and monitoring of controlled substances.

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. (A complete biography can be found online at www.NetCE.com.)

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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INTRODUCTION

Substance use disorders continue to be an important health issue in the United States. The fifth edition (text revision) of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5-TR) includes criteria for substance use disorder involving alcohol; cannabis; hallucinogens; inhalants; opioids; sedatives, hypnotics, or anxiolytics; stimulants; tobacco (nicotine); and other (or unknown) substances [1]. Excluding tobacco use disorder, the most common substance use disorders in the United States are [2]:

- Alcohol use disorder (29.5 million)
- Cannabis use disorder (16.3 million)
- Prescription opioid use disorder (5.0 million)
- Methamphetamine use disorder (1.6 million)

Substance use disorders can lead to significant problems in all aspects of a person's life, and appropriate assessment and management of substance use is a priority in patient care.

The presence of substance use disorders can complicate the treatment or management of comorbid medical conditions. Given the ongoing prescription opioid (and illicitly manufactured fentanyl) use and overdose epidemic in the United States and the widespread incidence of chronic pain, opioid prescribing and optimum safe pain management is a public health concern. All clinicians should have good knowledge of the available options for substance use disorder treatment and for safe opioid prescribing and dispensing.

Coordinated care is critical to achieve positive outcomes. Coordinating treatment for comorbidities, including mental health conditions, is an important part of treating substance use disorders and pain alike.

SUBSTANCE USE DISORDER SCREENING AND DIAGNOSIS

According to the 2021 National Survey on Drug Use and Health, 46.3 million Americans 12 years of age or older had a substance use disorder in the past year [2]. Substance use disorders are treatable, chronic diseases characterized by a problematic pattern of use of a substance or substances leading to impairments in health, social function, and control over substance use. It is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite harmful consequences. These disorders range in severity and can affect people of any race, gender, income level, or social class.

RISK FACTORS

Researchers who study risk factors have developed models of how known risk factors may interact to create pathways that lead to substance use disorders. Of course, not all persons who use drugs regarded as having a high liability of misuse end up becoming addicted to the drug.

Genetic Predisposition

Research has shown that genetic factors play a strong role in whether a person develops a substance use disorder, accounting for 40% to 60% of the risk [3; 4; 5]. In fact, family transmission of substance use disorder, particularly alcohol use disorder, has been well established. Individuals who have relatives with substance use disorder are at three- to five-times greater risk of developing substance use disorder than the general population. The presence of substance use disorder in one or both biologic parents is more important than the presence of substance use disorder in one or both adoptive parents. The genetic risk increases with the number of relatives with substance use disorder and the closeness of the genetic relationship [5]. However, most children of parents with substance use disorder do not develop disorders, and some children from families where substance use is not a problem develop disorders when they get older.

Children with Conduct Problems

One model focuses on children who have temperaments that make it difficult for them to regulate their emotions and control their impulses. Clearly, these children are difficult to parent, and if one or both of their parents have a substance use disorder, it is likely that they will be poorly socialized and have trouble getting along in school [6; 7]. Poor academic performance and rejection by more mainstream peers at school may make it more likely for these children to join peer groups where drinking and other risky behaviors are encouraged. Parents with substance use disorders will likely not monitor their children closely and will lose control over them at an early age. These children will begin using substances early, often before 15 years of age [8]. If such a child is genetically predisposed to substance use disorders, these environmental factors may further increase the tendency [9].

Stress and Distress

Another model of risk factors leading to substance use disorder focuses on substance use to regulate inner distress [10]. Some children have temperaments that make them highly reactive to stress and disruption. Regardless of the child's family environment, he or she maintains higher levels of inner distress (anxious and depressed feelings) than other children. When they first drink or use a substance, the inner distress dissipates for a while. This leads to more substance use and may lead to substance use disorder. More research is required before the role of stress as a risk factor in alcohol use disorders is understood.

SCREENING AND ASSESSMENT TOOLS CHART						
Tool	**Substance Type**		**Patient Age**		**Administration Method**	
	Alcohol	**Drugs**	**Adults**	**Adolescents**	**Self-Administered**	**Clinician-Administered**
Screening Tools						
Screening to Brief Intervention (S2BI)	X	X		X	X	X
Brief Screener for Alcohol, Tobacco, and other Drugs (BSTAD)	X	X		X	X	X
Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS)	X	X	X		X	X
Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide (NIAAA)	X			X		X
Opioid Risk Tool – OUD (ORT-OUD) Chart		X	X		X	
Assessment Tools						
Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS)	X	X	X		X	X
CRAFFT	X	X		X	X	X
Drug Abuse Screen Test (DAST-10)[a]		X	X		X	X
Drug Abuse Screen Test (DAST-20: Adolescent version)[a]		X		X	X	X
Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide (NIAAA)	X			X		X
[a]Tools with associated fees						
Source: [14]						*Table 1*

Adverse childhood experiences, particularly sexual abuse, family rejection, and parental neglect, are independent risk factors for substance use disorders [11]. Adverse childhood experiences are linked with depression in adulthood, which itself is a risk factor for substance use disorder. This correlation can be modulated by resilience, which can also be a result of adverse childhood experiences.

Other Mental Disorders

Mental disorders can contribute to substance use and substance use disorders. Certain psychiatric disorders, including anxiety, depression, or post-traumatic stress disorder, have been linked to substance misuse, likely a form of self-medication. Additionally, brain changes in people with mental disorders may enhance the rewarding effects of substances, making it more likely they will continue to use the substance [12].

Environmental Stimuli

The expected drug effect and the setting of use (context of administration) play important roles in the social learning of drug use. Opioids and other drugs that increase dopamine turnover lead to conditional responses, and use may become conditioned to the activities of daily living. As a result, environmental stimuli can become powerfully associated with substance use, which can trigger cravings for the drug [13]. The visibility of pharmaceutical marketing and advertising of medications may also play a role by changing the attitudes toward ingestion of these agents [13]. For youth, a social learning aspect to drug use is likely, based on the modeling of drug use by adults in their families and social networks [13].

SCREENING

A variety of screening and assessment tools are available, with applicability for various substances, patient populations, and screening environments (***Table 1***).

The Tobacco, Alcohol, Prescription medication, and other Substance Use (TAPS) Tool is validated for use with adults to generate a risk level for each substance class. It can be self-administered or conducted via clinician interview and combines screening and brief assessment of past 90-day problematic use into one tool [14]. The TAPS Tool has two components. The first component (TAPS-1) is a four-item screen for tobacco, alcohol, illicit drugs, and non-medical use of prescription drugs. If an individual screens positive on TAPS-1 (i.e., reports other than "never"), the tool will automatically begin the second component (TAPS-2), which consists of brief substance-specific assessment questions to arrive at a risk level for that substance. Clinicians are encouraged to provide positive feedback to patients who screen negative and support their choice to abstain from substances. The tool can be accessed online at https://nida.nih.gov/taps2/#/.

DIAGNOSIS

As noted, the DSM-5-TR defines substance use disorder as a problematic pattern of substance use, leading to clinically significant impairment or distress. While criteria are outlined for specific substances in the DSM-5-TR, the components are generally the same regardless of substance used. The diagnosis of substance use disorder is made by meeting two or more criteria in a one-year period [1]:

- Substance taken in larger amounts or over a longer period than was intended
- A persistent desire or unsuccessful efforts to cut down or control use
- Excessive time spent to obtain, use, or recover from using the substance
- Craving, an intense urge to use
- Substance use interferes with obligations
- Continued use despite life disruption
- Reduction or elimination of important activities due to use
- Recurrent use in physically hazardous situations
- Continued use despite physical or psychologic problems
- Tolerance
  - Need for increased doses of the substance for the desired effect
  - A markedly diminished effect with continued use of the same amount
- Withdrawal

In the case of opioid use disorder, the criteria for tolerance and withdrawal are not considered to be met for those taking opioids solely under appropriate medical supervision.

SUBSTANCE USE DISORDER TREATMENT

All substance use disorder treatment plans should reflect the patient's most important goals and establish measurable and achievable steps toward achieving those goals. As such, all treatment plans will be individualized and created in collaboration with the patient. This recovery roadmap also requires that clinicians communicate with clear, nonstigmatizing language regarding the patient's condition and options.

TREATMENT PLANNING

Assessing Readiness to Change

Readiness to Change is Dimension 4 of the American Society of Addiction Medicine's (ASAM's) Six Dimensions of Multidimensional Assessment (also known as the ASAM Criteria) that is the standard for placement, continued stay, transfer, or discharge of patients with substance use disorder and co-occurring conditions [15]. Several factors influence a person's readiness and ability to change behaviors. It is useful to help patients to weigh the risks of continued substance use and benefits of decreasing or eliminating substance use. Healthcare professionals can help motivate the patient to become ready for treatment if the patient appears ready to change.

Is the patient ready to change? The role of motivation is an important part of changing behavior.

Motivational Interviewing

Motivational interviewing is a method of counseling designed to enhance patients' motivation to change by helping them explore and resolve their ambivalence about making the change [16]. It is a collaborative, non-confrontational, "guiding" approach. In substance use disorder, motivational interviewing utilizes active listening to understand how the patient feels about his or her substance use in an effort to uncover any ambivalence [17]. The healthcare provider elicits the patient's own views regarding consequences of continuing to use and benefits of quitting and asks permission to share additional information on risks when necessary. Goals are developed collaboratively, based on the patient's current readiness to change. Originally developed as an intervention for alcohol use disorder, it has shown promise as a successful strategy for other substances as well.

PSYCHOSOCIAL THERAPY

Treatment of substance use and dependence with psychosocial or behavioral therapy is based on the assumption that addictive behavior is developed and maintained by specific mechanisms [18]:

- Expectancies and modeling
- Reinforcing properties of the drug
- Secondary social reinforcement

The goal of these types of treatments is to modify drug-seeking and other behavioral aspects of drug dependency [19]. Psychosocial therapy and pharmacotherapy are not mutually exclusive; in fact, some drug therapies for substance abuse are considered useless without a psychosocial/behavioral component [18; 19].

Psychosocial therapies for substance use disorders can be divided into two broad categories. The first category consists of therapies that were originally developed for patients with anxiety and depression and modified for use with patients with substance use disorders. This group of therapeutic approaches includes cognitive-behavioral therapy (CBT), the behavioral therapies, and interpersonal therapy. The second group of psychosocial therapies was developed explicitly for patients with substance use disorders and includes motivational interviewing and motivation enhancement therapy [19; 20]. All psychotherapies are intended to be delivered in a supportive, empathic manner that minimizes confrontation.

EVIDENCE-BASED PRACTICE RECOMMENDATION

For patients with alcohol use disorder, the Department of Veterans Affairs Work Group recommends offering one or more of the following interventions, considering patient preference and provider training/competence:

- Behavioral couples therapy for alcohol use disorder
- Cognitive-behavioral therapy for substance use disorders
- Community reinforcement approach
- Motivational enhancement therapy
- 12-step facilitation

(https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPG.pdf. Last accessed April 27, 2023.)

Strength of Recommendation: Strong for

Drug counseling is a widely used therapy approach with patients with substance use disorders. It consists of a focus on abstinence, problem solving, and 12-step orientation and involvement. Drug counseling is usually provided by counselors who have a certificate in addiction counseling. A fair number of addiction counselors are themselves recovering from alcohol and/or substance use disorders [20].

Contingency Management

There is considerable evidence that substance use is sensitive to the application of contingencies. Contingencies occur on a spectrum from contrived to naturalistic. Contingency management and vouchers are examples of contrived interventions, while 12-step programs are examples of naturalistic interventions [21]. Contrived contingencies may be effective in initially engaging patients in abstinence, but relapse to drug use may occur following removal of the reinforcer. In contrast, naturalistic contingencies are more likely to maintain the initial gains made by the patient and to facilitate the sustained change of behavior over time [22].

The goal of contingency management interventions is to increase the opportunity cost of substance use by arranging an environment where drug use results in the forfeiture of a predetermined item or privilege, referred to as an alternate reinforcer [23]. Treatment with a contingency management component was first used with cocaine-abusing methadone patients, a highly suitable population for two reasons: cocaine abuse is prevalent among patients with opioid use disorder receiving methadone maintenance, and methadone patients are required to report to the clinic daily to receive their medication under staff supervision. Daily clinic appointments are often considered a significant constraint on employment, travel, and other activities. Patients who are able to abstain from drugs of abuse, as measured by a urine drug screen, may be allowed several days of take-home methadone doses, which can act as a behavioral contingent [24]. Several studies have shown that this contingent condition has led to greater treatment retention and reductions in cocaine use than those found in comparison treatment conditions, although this effect dissipates with longer-term follow-up [22; 25; 26; 27].

Community Reinforcement

Community reinforcement approaches are biopsychosocial interventions designed to engage and change the lifestyle of the drug abuser by addressing the role of environmental cues and alternative reinforcers in influencing behavior. The theoretical basis of the community reinforcement approach is that substance abuse is maintained by substance-related reinforcers as well as by the absence of competing alternative reinforcers. The primary goal of the community reinforcement approach is to build and strengthen relationships, recognize appropriate leisure activities, and identify vocational interests of the patient to provide competing reinforcement with substance use and the drug-using lifestyle [28]. The community reinforcement approach aims to increase abstinence by increasing or highlighting the opportunity cost of relationships and social support the patient stands to lose through drug use [22]. In addition to integrating cognitive-behavioral and, in some cases, pharmacologic approaches, community reinforcement approaches may also include the use of vouchers, whereby tokens are given to the patient for producing substance-free urine samples, which are then used to purchase goods and services desired by the patient.

A review of four studies utilizing a community reinforcement approach with patients with substance use disorder found evidence that a community reinforcement approach employing abstinence-contingent incentives in the form of vouchers was more effective in promoting abstinence than community reinforcement approaches using noncontingent incentives and usual care. Patients assigned to community reinforcement incorporating abstinence-contingent incentives experienced a greater reduction in disease severity as measured by the Addiction Severity Index than comparison groups [28]. Despite early, promising reports of community reinforcement with patients with alcohol use disorder and evidence that patients receiving community reinforcement approaches have demonstrated more favorable drug use outcomes than patients receiving standard outpatient counseling, a community reinforcement approach is seldom used because of the relatively high cost and labor intensity [19; 29].

Motivational Interventions

Motivational interventions for substance use disorders stem from the theory that targeting and enhancing motivation to quit drugs will increase positive outcome; positive outcome is increased when motivation comes internally rather than when it is externally imposed. Specifically, motivational enhancement therapy is based on the Transtheoretical Stages of Change Theory, which postulates that patients pass through a series of stages of thought, planning, and action in the process of behavior change [30]. Motivational enhancement therapy is

intended to enhance motivation and commitment to change, activate patient resources, and facilitate movement along the readiness-to-change spectrum [31]. Motivational enhancement therapy helps patients build internal motivation through the resolution of issues related to ambivalence. The therapeutic approach is characterized by nonconfrontive, nonjudgmental interviewing that helps the patient consider the pros and cons of change. Motivational enhancement therapy also strives to enhance patient self-efficacy [30]. Motivational enhancement therapy seems to be more effective in patients with low initial levels of motivation when used for patients with substance use disorder. It tends to result in less relapse to use and fewer total days of use [32].

Coping and Social Skill Training

Coping and social skill training (CSST) evolved from social learning theory and is used to improve the inadequate coping skills found in many persons with substance use disorders, including deficits in regulation of emotion and in effectively coping with social situations. CSST addresses four primary areas [33]:

- Interpersonal skills
- Cognitive and affective regulation
- Coping skills to manage stressful life events
- Coping skills when substances or substance-related cues are encountered

An added emphasis on drug-related cues is used when CSST is employed with patients with certain substance use disorders (e.g., cocaine, opioids) [33].

CSST has incorporated these findings into the treatment approach used with patients with substance use disorders. Preliminary results indicate some benefit of substance-specific CSST in reducing frequency of substance use and increasing duration of abstinence, although these results have not been replicated in subsequent research [32; 33].

Drug Counseling

CBT is among the most frequently evaluated approaches used to treat substance use disorders [34; 35]. CBTs have been shown to be effective in several clinical trials of substance users [36]. Characteristics of CBTs include:

- Social learning and behavioral theories of drug abuse
- An approach summarized as "recognize, avoid, and cope"
- Organization built around a functional analysis of substance use (i.e., understanding substance use with respect to its antecedents and consequences)

Skill training focused on strategies for coping with craving, fostering motivation to change, managing thoughts about drugs, developing problem-solving skills, planning for and managing high-risk situations, and cultivating drug refusal skills

Basic principles of CBTs are that [37; 38]:

- Basic skills should be mastered before more complex ones are given.
- Material presented by the therapist should be matched to patient needs.
- Repetition fosters the development of skills.
- Practice is needed for mastery of skills.
- The patient is an active participant in treatment.
- Skills taught are general enough to be applied to a variety of problem areas.

Structured behavior therapy techniques can be effective components of substance use disorder treatment. Contingent incentive procedures are designed to enhance a patient's motivation to meet treatment goals by offering concrete rewards for specific performance outcomes.

Behavioral therapy techniques are often part of CBT. In this approach, substance use is believed to develop from changes in behavior and a reduction in opportunities for reinforcement of positive experience. The goal is to increase the person's engagement in positive or socially reinforcing activities. Techniques such as having patients complete a schedule of weekly activities, engaging in homework to learn new skills, role-playing, and behavior modification are used. Activity, exercise, and scheduling are major components of this approach based on the following:

- Patients with substance use disorders require motivation and skills to succeed in stopping drug use.
- Research has shown that drug abuse behavior can be reduced by offering contingent incentives for abstinence.
- The most striking successes have come from positive reinforcement programs that provide contingent incentives for abstinence using money-based vouchers as rewards.
- Research provides examples, but treatment providers may need to be creative in discovering reinforcers that can be used for contingency management in their own clinical settings.

Family therapy is a highly effective treatment for alcohol use disorder, especially in adolescents. While most treatments emphasize the individual as the target of intervention, the defining characteristic of family therapy is the transformation of family interactions. Repetitive patterns of family interactions are the focus of treatment. Changing these patterns results in diminished antisocial behavior including alcohol abuse. Family therapy can work with a broad range of family and social network populations. Family therapy approaches have developed specific interventions for engaging and keeping reluctant, unmotivated adolescents and family members in treatment.

MEDICATIONS USED IN THE TREATMENT OF SUBSTANCE USE DISORDERS					
Drug	**Dose Range**	**Typical Starting Dose**	**Potential Adverse Effects**	**Route(s)**	**DEA Schedule**
Opioid Use Disorder					
Buprenorphine/ naloxone (Bunavail, Suboxone, Zubsolv)	Buprenorphine: 0.7–24 mg/day Naloxone: 0.18–6 mg/day	4/1 mg/day	Pain, headache, nausea, diaphoresis	Buccal film, sublingual film, sublingual tablet	CIII
Methadone (Dolophine, Methadose, DISKETS)	20–120 mg/day	20–30 mg/day	Pruritus, constipation, cardiac abnormalities	PO, IV	CII
Naltrexone (Vivitrol)	PO: 25-50 mg/day IM: 380 mg/week	PO: 25 mg/day IM: 380 mg/week	Injection site reactions, anxiety, syncope	PO, IM	Not scheduled
Buprenorphine (Belbuca, Buprenex, Butrans, Probuphine, Sublocade)	SQ: 100–300 mg/month SL: 2–24 mg/day	SQ: 300 mg/month Implant: 4 implants SL: 2–4 mg/day	Few	Sublingual tablet, subdermal implant, SQ injection	CIII
Alcohol Use Disorder					
Acamprosate (Campral)	666 mg TID	666 mg TID	Diarrhea	PO	Not scheduled
Naltrexone (Vivitrol)	PO: 25–100 mg/day IM: 380 mg/month	PO: 50 mg/day IM: 380 mg/month	Injection site reactions, anxiety, syncope	PO, IM	Not scheduled
Disulfiram	125–500 mg/day	250 mg/day	Bitter taste, impotence, drowsiness	PO	Not scheduled
Tobacco Use Disorder					
Bupropion, sustained-release (Zyban)	150 mg daily or BID	150 mg/day	Weight loss, constipation, agitation, xerostomia, nausea	PO	Not scheduled
Nicotine	Gum: Up to a maximum 30 pieces/day Inhaler: 6–16 cartridges/ day Lozenge: Titrate to 1 lozenge every 4 to 8 hours Nasal spray: Maximum 80 sprays/day Patch: One patch/day for 8 weeks	Gum: 1 to 2 pieces/ hour (2 mg/piece) Inhaler: 6 cartridges/ day Lozenge: One lozenge every 1 to 2 hours Nasal spray: 1 spray in each nostril once or twice per hour Patch: One patch/day	Oral irritation, headache, dyspepsia, nasal discomfort, cough, rhinitis	PO, intranasal, transdermal	Not scheduled
Varenicline (Chantix)	1 mg BID up to 12 weeks	0.5 mg/day	Nausea, abnormal dreams, headache	PO	Not scheduled
BID = two times per day, DEA = Drug Enforcement Administration, IM = intramuscular, IV = intravenous, PO = oral, SL = sublingual, SQ = subcutaneous, TID = three times per day.					
Source: [39]					*Table 2*

PHARMACOTHERAPY FOR DETOXIFICATION AND ABSTINENCE

A variety of medications have been approved to assist in cessation of the use of opioids, alcohol, and nicotine (***Table 2***). Any time pharmacotherapy is initiated, is important that a collaborative, patient-centered approach is undertaken, with all members of the care team working together to best meet the needs of the specific patient. Unique, individual physiology and metabolism can impact medication pharmacodynamics; this should be considered in each treatment plan.

Alcohol Use Disorder

Several medications are available to help treat alcohol use disorder [40; 41]. Some are used for detoxification and others are used to prevent relapse. Research has shown that medications are most effective when used in conjunction with other therapies.

Disulfiram

Disulfiram, commonly known as Antabuse, was the first drug to be made available for the treatment of alcohol use disorder. It was approved for treatment of alcohol use disorder by the U.S. Food and Drug Administration (FDA) in 1951 and has been used safely and effectively for decades. It works by blocking an enzyme, aldehyde dehydrogenase, that helps metabolize alcohol. Taking even one drink while on disulfiram causes the alcohol at the acetaldehyde stage to accumulate in the blood. This produces nausea, vomiting, sweating, and even difficulty breathing. More alcohol in the patient's system produces more severe reactions (e.g., respiratory depression, cardiovascular collapse, unconsciousness, convulsions, death) [41; 42]. Patients must also be mindful of consuming even minute amounts of alcohol in foods, over-the-counter medications, mouthwash, and even topical lotions. Disulfiram can be effective for people who have completed alcohol withdrawal, are committed to staying sober, and are willing to take the medication under the supervision of a family member or treatment program [41]. Due to more modern and improved medication modalities, many clinicians prescribe disulfiram as a last-resort intervention. Although widely used, it is less clearly supported by clinical trial evidence [43; 44; 45].

The recommended dose for disulfiram is 250 mg/day, which can be increased to 500 mg based upon whether a patient experiences the disulfiram-ethanol reaction [46]. Doses may need to be reduced in patients older than 60 years of age [41]. Labeling for disulfiram includes several precautions regarding drug-drug interactions; therefore, caution should be used when prescribing it to older adults at risk for polypharmacy [41]. Due to the physiologic changes that occur with use, use of disulfiram is not recommended in patients with diabetes, cardiovascular or cerebrovascular disease, or kidney or liver failure. It also is contraindicated in the presence of psychoses and pregnancy and in those with high levels of impulsivity and suicidality [41].

Naltrexone

Naltrexone (ReVia) is an opioid antagonist that interferes with the rewarding or pleasurable effects of alcohol and reduces alcohol craving [47; 48; 49]. The exact mechanisms by which naltrexone induces the reduction in alcohol consumption observed in patients with alcohol use disorder is not entirely understood, but preclinical data suggest involvement of the endogenous opioid system [41]. Naltrexone has been shown to reduce alcohol relapses, decrease the likelihood that a slip becomes a relapse, and decrease the total amount of drinking [41]. The FDA approved the use of oral naltrexone in alcohol use disorder in December 1994 [41; 49]. In 2006, the FDA approved an extended-release injectable formulation, which is indicated for use only in patients who can refrain from drinking for several days prior to beginning treatment [41]. In 2010, the FDA approved the injectable naltrexone for the prevention of relapse to opioid dependence following opioid detoxification [41].

After a complete history, physical exam, and laboratory testing, most patients are started on 50 mg orally per day [39]. For most patients, this is the safe and effective dose of naltrexone. However, in a four-month study period, the COMBINE study demonstrated efficacy of naltrexone at a dose of 100 mg daily [50]. Some treatment providers give patients a naltrexone identification card or ask them to order a MedicAlert bracelet that clearly indicates that they are maintained on an opioid antagonist, so if they need an opiate drug or medication for pain relief, the dose of the pain medication can be adjusted higher. Meta-analyses have revealed that approximately 70% of previous clinical trials that measured reductions in "heavy or excessive drinking" demonstrated an advantage for prescribing naltrexone over placebo [51]. In another trial, naltrexone was determined to have the greatest impact on reducing daily drinking when craving for alcohol was highest [52]. The approved dose of the extended-release formulation is 380 mg IM once per month. Pretreatment with oral naltrexone is not required before induction onto extended-release injectable naltrexone [41].

The most common side effects of naltrexone are light-headedness, diarrhea, dizziness, and nausea. Pain or tenderness at the injection site is a side effect unique to the extended-release injectable formulation [41]. Most side effects tend to disappear quickly in most patients. Naltrexone is not recommended for patients with acute hepatitis or liver failure, for adolescents, or for pregnant or breastfeeding women [41; 50]. Weight loss and increased interest in sex have been reported by some patients. In general, patients maintained on opioid antagonists should be treated with nonopioid cough, antidiarrheal, headache, and pain medications. The patient's family or physician should call the treating physician if questions arise about opioid blockade or analgesia. It is important to realize that naltrexone is not disulfiram; drinking while maintained on naltrexone does not produce side effects or symptoms.

Naltrexone works best when it is used in the context of a full spectrum of treatment services, possibly including traditional 12-step fellowship-based treatments. Studies show also that naltrexone is effective when coupled with CBT. Patients receiving medical management with naltrexone, CBT, or both fared better on drinking outcomes [50].

Acamprosate

Acamprosate (Campral) is a synthetic compound that has a chemical structure similar to that of the naturally occurring amino acid neurotransmitters taurine and gamma-aminobutyric acid (GABA) [39]. Because chronic alcohol use is associated with decreased GABA and glutamate activity, a hyperexcitable glutamate system is one possible alcohol withdrawal

mechanism. Glutamate systems may become unstable for 12 months after a person stops drinking. In a review of published, double-blind, placebo-controlled clinical trials evaluating the safety and efficacy of acamprosate in the treatment of alcohol use disorder, Mason reported that acamprosate appeared to improve treatment completion rate, abstinence rate and/or cumulative abstinence during treatment, and time to first drink, than placebo [53]. The effect on abstinence, combined with an excellent safety profile, lend support to the use of acamprosate across a broad range of patients with alcohol use disorder [54]. It is important to note that medication in combination with therapies can improve outcomes.

In July 2004, after many years of safe use in Europe and around the world, the FDA approved the use of acamprosate for the maintenance of alcohol abstinence [49]. As in the case of naltrexone, acamprosate reduces the reinforcing (pleasurable) effects of alcohol to reduce craving. Oral dosing is two 333-mg delayed-release tablets three times daily [39; 41]. Common side effects include diarrhea, anxiety, insomnia, nausea, dizziness, and weakness. Some research indicates that acamprosate may worsen depression and/or suicidal ideation; so, patients with a history of major depression should be monitored closely or prescribed a different medication [39]. Acamprosate is contraindicated in patients with severe renal impairment [39; 41]. Due to risk of diminished renal function in patients 65 years of age and older, baseline and frequent renal function tests should be performed in this population. Dose reductions also may be necessary [41].

Baclofen

Baclofen is a GABA agonist that may prove to be a unique therapeutic alternative to reduce alcohol craving and consumption. In a small, 12-week trial, patients with alcohol use disorder were given 10 mg of baclofen three times daily paired with motivational enhancement therapy. Patients experienced a reduction in number of drinks, drinking days, anxiety, and craving [55]. In a study of patients with alcohol use disorder and liver cirrhosis, baclofen was also found to work favorably in maintenance of alcohol abstinence. Seventy-one percent of baclofen-treated patients maintained abstinence as compared with 29% of the placebo group [56]. A 2018 meta-analysis of 12 randomized controlled trials that compared the efficacy of baclofen to placebo found that baclofen was associated with higher rates of abstinence than placebo but that its effects were not superior to placebo in increasing the number of abstinent days or in decreasing heavy drinking, craving, depression, or anxiety [57].

Anticonvulsants

Research has demonstrated that topiramate is efficacious in decreasing heavy drinking among individuals with alcohol use disorder [58]. In a controlled study, topiramate produced significant and meaningful improvement in a wide variety of drinking outcomes [59]. Topiramate may suppress the craving and rewarding effects of alcohol [60]. In a double-blind, controlled trial, 150 patients with alcohol use disorder were randomized to escalating doses of topiramate (25–300 mg/day) or placebo. Those on topiramate had a reduction in self-reported drinking (number of drinks and drinking days), alcohol craving, and plasma gamma-glutamyl transferase (an indicator of alcohol consumption) [61]. Side effects of topiramate include numbness in the extremities, fatigue, confusion, paresthesia, depression, change in taste, and weight loss. Use of topiramate for alcohol use disorder is off-label [39].

Carbamazepine has proven effective for treating acute alcohol withdrawal [62]. Its side effects include nausea, vomiting, drowsiness, dizziness, chest pain, headache, trouble urinating, numbness in extremities, liver damage, and allergic reaction [39]. In a 12-month, double-blind, placebo-controlled trial, 29 patients were assigned to carbamazepine three times daily (to reach an average blood level of 6 mg/liter) or placebo. Those treated with carbamazepine showed a delay in time to first drink and a decrease in number of drinks and drinking days [63].

Oxcarbazepine is a carbamazepine derivative, with fewer side effects and contraindications, used to prevent relapse in patients with alcohol use disorder by blocking alcohol withdrawal [62]. A group of 84 patients with alcohol use disorder following detoxification were randomized to 50 mg naltrexone, 1,500–1,800 mg oxcarbazepine, or 600–900 mg oxcarbazepine for 90 days. Approximately 58.6% of the high-dose oxcarbazepine patients remained alcohol-free, a significantly larger number as compared to the low-dose (42.8%) and naltrexone groups (40.7%) [64].

Opioid Use Disorder

Any treatment for opioid use disorder must take into consideration the chronic relapsing nature of opioid dependence, characterized by a variable course of relapse and remission in many patients. Treatments should emphasize patient motivation, psychoeducation, continuity of care, integration of pharmacotherapy and psychosocial support, and improved liaison between the treatment staff and the judicial system. Pharmacotherapy must be offered in a comprehensive healthcare context that also addresses the psychosocial aspects of dependence [65]. Patients with opioid use disorder frequently suffer from physical and psychiatric disorders, and targeted interventions of psychiatric comorbidity are essential in improving treatment outcome for these patients [65]. Polysubstance abuse is the rule rather than the exception in opioid use disorder, and concurrent use of other substances should be carefully monitored and treated when necessary [65]. Incarceration should never automatically result in discontinuation of an existing treatment; imprisonment offers a window of opportunity to initiate or restart treatment with a necessary continuation after release [65].

Crisis Intervention

In response to acute overdose, the short-acting opioid antagonist naloxone is considered the criterion standard. Naloxone is effective in reversing respiratory depression and coma in

patients who have overdosed. There is no evidence that subcutaneous or intramuscular use is inferior to intravenous naloxone. This prompted discussion of making naloxone available to the general public for administration outside the healthcare setting to treat acute opioid overdose, and in 2014, the FDA approved naloxone as an autoinjector dosage form for home use by family members or caregivers [66]. The autoinjector delivers 0.4 mg naloxone intramuscularly or subcutaneously. The autoinjector comes with visual and voice instruction, including directions to seek emergency medical care after use [66]. In 2015, the FDA approved intranasal naloxone after a fast-track designation and priority review. Intranasal naloxone is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. It is available in a ready-to-use 2-mg, 4-mg, or 8-mg single-dose sprayer [67; 68; 69]. In 2023, the FDA approved 4-mg nasal spray naloxone for over-the-counter use [173].

According to the World Health Organization, people likely to witness an opioid overdose should have access to naloxone and be instructed in its administration to enable them to use it for the emergency management of suspected opioid overdose.

(https://www.who.int/publications/i/item/9789241548816. Last accessed April 27, 2023.)

Strength of Recommendation/Level of Evidence: Strong/very low

Harm Reduction

Harm reduction measures are primarily employed to minimize the morbidity and mortality from opioid abuse and to reduce public nuisance [2; 70]. As a part of this effort, measures to prevent and minimize the frequency and severity of overdoses have been identified. Enrollment in opioid substitution therapy, with agents such as methadone and buprenorphine, substantially reduces the risk of overdose as well as the risk for infection and other sequelae of illicit opioid use [2; 70].

Detoxification

The three primary treatment modalities used for detoxification are opioid agonists, non-opioid medications, and rapid and ultra-rapid opioid detoxification [71]. The most frequently employed method of opioid withdrawal is a slow, supervised detoxification during which an opioid agonist, usually methadone, is substituted for the abused opioid [72]. Methadone is the most frequently used opioid agonist due to the convenience of its once-a-day dosing [71]. Methadone is highly bound to plasma proteins and accumulates more readily than heroin in all body tissues. Methadone also has a longer half-life, approximately 22 hours, which makes withdrawal more difficult than from heroin. Substitution therapy with methadone has a high initial dropout rate (30% to 90%) and an early relapse rate. Alternative pharmacologic detoxification choices include clonidine (with or without methadone), midazolam, trazodone, or buprenorphine [72].

Many opioid withdrawal symptoms, such as restlessness, rhinorrhea, lacrimation, diaphoresis, myosis, piloerection, and cardiovascular changes, are mediated through increased sympathetic activation, the result of increased neuron activity in the locus coeruleus. Non-opioid agents (such as clonidine), which inhibit hyperactivation of noradrenergic pathways stemming from the locus coeruleus nucleus, have been used to manage acute withdrawal [72; 73]. The first non-opioid treatment approved for the management of opioid withdrawal symptoms is lofexidine [74]. In studies, patients treated with lofexidine reported less severe withdrawal symptoms and were more likely to complete treatment.

However, some withdrawal symptoms, including anxiety and myalgias, are resistant to clonidine; benzodiazepines and nonsteroidal anti-inflammatory drugs (NSAIDs) may be necessary to treat these symptoms. To mitigate withdrawal symptoms and assist in detoxification, alpha2-agonists, opioid agonist-antagonists, benzodiazepines, and antidepressants have been used [72].

Agonist Replacement Therapy

The goal of opioid replacement therapy is to reduce illicit drug use and associated health risks, with secondary goals of reducing unsafe sexual practices, improving vocational and psychosocial functioning, and enhancing quality of life [71]. The theoretical basis of opioid replacement stems from the finding that chronic opioid use results in an endogenous opioid deficiency as a result of the down-regulation of opioid production. This creates overwhelming cravings and necessitates interventions that shift the dependent patient's attention and drive from obsessive preoccupation with the next use of opioids to more adaptive areas of focus, such as work, relationships, and non-drug leisure activities [71].

For patients with opioid use disorder, the Department of Veterans Affairs Work Group recommends offering one of the following medications, considering patient preferences: buprenorphine/naloxone or methadone (in an opioid treatment program).

(https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPG.pdf. Last accessed April 27, 2023.)

Strength of Recommendation: Strong for

Methadone is now the most inexpensive and empirically validated agent available for use in opioid replacement therapy. Studies have shown one-year treatment retention rates of 80%, with significant reductions in illicit opioid use [71].

Treatment is initiated with a dose of 25–30 mg and is gradually titrated in 5- to 10-mg increments per day to a desired range of 60–120 mg. Low-dose treatment is associated with less positive outcomes than doses of 60–120 mg/day or greater [71; 75]. One published review of efficacy literature concluded that high doses of methadone (>50 mg daily) are more effective than low doses (<50 mg daily) in reducing illicit opioid use. This may be due to the increased availability of highly pure heroin [75]. Additionally, high doses of methadone are more effective than low doses of buprenorphine (<8 mg daily). High dosages of methadone are comparable to high dosages of buprenorphine (>8 mg daily) on measures of treatment retention and reduction of illicit opioid use [65]. Methadone is contraindicated for the following patients [73]:

- Those with known hypersensitivity to methadone hydrochloride
- Those experiencing respiratory depression
- Those with acute bronchial asthma or hypercapnia
- Those with known or suspected paralytic ileus

EVIDENCE-BASED PRACTICE RECOMMENDATION

When considering initiation of methadone, the American Pain Society recommends that clinicians perform an individualized medical and behavioral risk evaluation to assess risks and benefits of methadone, given methadone's specific pharmacologic properties and adverse effect profile.

(https://www.jpain.org/article/S1526-5900(14)00522-7/fulltext. Last accessed April 27, 2023.)

Strength of Recommendation/Level of Evidence: Strong/low

Buprenorphine offers several advantages over methadone, including lower cost, milder withdrawal symptoms following abrupt cessation, lower risk of overdose, and longer duration of action, allowing alternate-day dosing [71; 76]. Identifying subpopulations of opioid addicts who differentially respond to buprenorphine versus methadone has not been clearly established. However, patients with less chronic and less severe heroin dependence benefit more fully from buprenorphine than from a pure opioid agonist like methadone [71].

The transition to buprenorphine from long-acting opioids is difficult [77]. The ASAM warns that diversion and misuse are possible with buprenorphine, as is physical dependence. Respiratory depression may occur if buprenorphine is used with central nervous system depressants including alcohol, other opioids, and illicit drugs. Neonatal withdrawal has also been reported after use of buprenorphine during pregnancy. Buprenorphine is not recommended for patients with severe hepatic impairment [73].

Higher doses of buprenorphine (12 mg or greater) are more effective than lower doses in reducing illicit opioid use, with some studies reporting similar efficacy to methadone on major treatment-outcome measures. The primary advantage of buprenorphine over methadone is its superior safety profile [77].

Slow-release formulations of morphine that are effective with once-daily dosing are a viable alternative in the treatment of opioid dependence. These formulations considerably delay time to peak concentration after oral administration, resulting in delayed onset of action and making the reinforcing effects very weak when it is administered orally. Several trials have suggested that slow-release morphine has approximately equal efficacy with methadone; however, there is no definitive evidence of this effect [77; 78; 79]. Slow-release oral morphine may be a viable alternative for patients who are intolerant to methadone [80].

Tobacco Use Disorder

The first-line pharmacologic interventions for smoking cessation are nicotine-replacement therapy (NRT), bupropion, and varenicline [81; 82]. However, no pharmacotherapy has been approved for use among pregnant or nursing women.

Bupropion

Bupropion is an atypical antidepressant that has both dopaminergic and adrenergic actions [83]. In 1998, the slow-release preparation of bupropion became available as a prescription item specifically for smoking cessation, with the trade name Zyban. This treatment could be appropriate for smokers who do not wish to use an NRT or for those whose treatment with NRT has failed. Unlike NRT, smokers begin bupropion treatment one week prior to cessation. The suggested dosage is 300 mg/day, and the duration of treatment is 7 to 12 weeks [84]. A double-blind, placebo-controlled trial randomized patients to placebo or sustained-released bupropion (50 mg twice a day, 150 mg once a day, or 150 mg twice a day) and treated them for six weeks. Smokers with active depression were excluded, though smokers with a history of depression were not. The cessation rates at the end of therapy were 10.5%, 13.7%, 18.3%, and 24.4%, respectively. Follow-up at one year suggested a continued benefit of bupropion therapy [85]. Data from a study of bupropion combined with transdermal nicotine showed high long-term quit rates with the combination therapy [86]. Discontinuation of treatment may be appropriate for individuals unable to achieve significant progress after seven weeks, as success after this point is unlikely [39].

Varenicline Tartrate

Another effective non-nicotine therapy for smoking cessation is varenicline tartrate, a partial agonist selective for nicotine acetylcholine receptor subtypes. Released in 2006, varenicline is available in monthly dose packs (0.5 mg and 1 mg tablets) and is approved for a 12-week course of treatment [82]. Patients able to quit smoking may continue the therapy for an additional 12 weeks for increased likelihood of long-term cessation and even up to a year in certain cases, to prevent relapse; however, medication should be stopped and patients should be reas-

sessed if the intervention has not led to smoking cessation within the initial 12 week timeframe [39; 87; 88]. Clinical trials reveal that varenicline may be favorable to bupropion for abstinence (44% versus 30%); the medication has also been shown to help at least 20% of patients remain smoke-free for up to one year [89; 90]. Recognizing that cessation success rates increase when pharmacologic and behavioral therapies are combined, the manufacturer urges patients to combine use of varenicline with a behavioral support plan. Co-administration of varenicline and transdermal nicotine may exacerbate incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue. One study found varenicline alone to be more effective than other treatment options, while a meta-analysis study found that combination therapy (varenicline and NRT) was more effective than varenicline alone [91; 92]. In 2021, the manufacturer of Chantix, a brand of varenicline, halted production of varenicline due to unacceptably high levels of nitrosamines; however, this issue was considered resolved by May 2022 [93]. In addition, all lots of 0.5-mg and 1-mg tablets of Chantix were subject to a voluntary recall. However, the FDA does not recommend that patients halt use of varenicline, and generic formulations and other brands remained available.

Other Options

The two second-line drugs for smoking cessation are clonidine and nortriptyline [81]. Clonidine is an antihypertensive medication that is administered orally or transdermally. It appears to increase the smoking cessation rate by approximately 11%; however, clonidine is known to produce such side effects as dry mouth, dizziness, sedation, and orthostatic hypotension [39; 94]. Clonidine has not been approved by the FDA for smoking cessation but has been used with individuals who have failed NRT or bupropion [39]. Nortriptyline is a tricyclic antidepressant that has been used to assist smoking cessation, although this is an unlabeled use [39]. A 12% improvement in cessation over controls has been reported, but the limited number of trials, combined with the adverse side effects (e.g., dry mouth, weight gain, constipation, drowsiness, sexual problems), makes nortriptyline a second-line intervention [81]. Several controlled trials have failed to show any benefit for either agent [39].

POLYSUBSTANCE USE

Despite the increased prevalence of individuals using multiple substances at the same time, limited research exists on evidence-based treatment practices that have demonstrated improved outcomes for individuals who use more than one substance [95]. Therefore, there is a need to identify and assess the effectiveness of treatment practices so that clinicians and organizations have the necessary resources and evidence-based practices to assist this population.

The Substance Abuse and Mental Health Services Administration (SAMHSA) has identified three evidence-based practices that engage and improve outcomes for individuals with concurrent substance use and concurrent substance use disorders [95]:

- FDA-approved pharmacotherapy together with counseling to treat:
  - Alcohol and cocaine dependence
  - Cocaine and opioid dependence
- Contingency management together with FDA-approved pharmacotherapy and counseling to treat:
  - Cocaine and opioid use and dependence
  - Cocaine dependence and alcohol and opioid use
- Twelve-step facilitation therapy together with FDA-approved pharmacotherapy and counseling to treat:
  - Cocaine and opioid dependence
  - Opioid and other substance dependence

CO-OCCURRING MENTAL DISORDERS

In the United States, 7.7 million adults have co-occurring mental and substance use disorders. Of the 20.3 million adults with substance use disorders, 37.9% also had mental illnesses. Among the 42.1 million adults with mental illness, 18.2% also had substance use disorders [96]. No specific combinations of mental and substance use disorders are defined uniquely as co-occurring disorders, but the most common mental disorders seen in substance use disorder treatment include [96]:

- Anxiety and mood disorders
- Schizophrenia
- Bipolar disorder
- Major depressive disorder
- Conduct disorders
- Post-traumatic stress disorder
- Attention deficit hyperactivity disorder (ADHD)

Patients with comorbid disorders demonstrate poorer treatment adherence and higher rates of treatment dropout than those without mental illness, which negatively affects outcomes [97]. Integrated treatment for comorbid drug use disorder and mental illness has been found to be consistently superior compared with separate treatment of each diagnosis. Integrated treatment of co-occurring disorders often involves using CBT strategies to boost interpersonal and coping skills and using approaches that support motivation and functional recovery.

Assessment

It is important to assess patients with substance use disorder for other psychiatric and substance use disorders. For example, alcohol and cocaine use disorders are frequent comorbidities in patients with opioid use disorder and can aggravate depressive symptoms [73; 99]. Bipolar illness is rare but has substantial treatment implications. Anxiety disorders frequently co-occur with depression, and traumatic experiences and post-traumatic stress disorder are common and should be thoroughly evaluated and treated [98; 99]. Independent disorders are psychiatric conditions occurring during periods of sustained abstinence or having an onset before the substance use disorder. A positive family history can aid in identifying an independent psychiatric disorder.

Comprehensive assessment tools can reduce the chance of a missed or incorrect diagnosis. Patients with psychiatric comorbidities often exhibit symptoms that are more persistent, severe, and resistant to treatment compared to patients who have either disorder alone [100; 101; 102; 103]. Assessment is critical to identify concomitant medical and psychiatric conditions that may need immediate attention and require transfer to a higher level of care [73]. The ASAM recommends that clinicians also assess social and environmental factors to identify facilitators and barriers to treatment, specifically to pharmacotherapy [73].

Treatment Approach

Treatment should initially focus on stabilization of the patient's substance use disorder, with an initial goal of two to four weeks abstinence before addressing comorbidities. Patients who persistently display symptoms of a psychiatric disorder during abstinence should be considered as having an independent disorder and should receive prompt psychiatric treatment [104].

Although depressive symptoms often improve following treatment admission, significant symptoms will persist in some patients [98]. Antidepressant medications can be effective in patients dually diagnosed with substance use disorder and depression when used at adequate doses for at least six weeks [105]. Factors emphasizing prompt antidepressant treatment include greater severity of depression, suicide risk, and co-occurring anxiety disorders [98].

Selective serotonin reuptake inhibitors (SSRIs) are generally safe and well-tolerated, but clinical trials with these agents in methadone patients have been negative [98]. Therefore, SSRIs may be considered first-line treatment based on their safety profile, but if the patient does not respond, then tricyclic antidepressants or newer generation agents should be considered. SSRIs in combination with CBT have been found to be highly effective for treating clients with comorbid depression [106]. More stimulating antidepressants, such as venlafaxine and bupropion, may be suitable in patients with prominent low energy or past or current symptoms consistent with ADHD [98].

The utility of nonpharmacologic treatments should be emphasized. Psychosocial therapies are as effective as pharmacotherapy in the treatment of mild-to-moderate depressive and anxiety symptoms. Treatment of personality disorders is nonpharmacologic [104]. If depression persists, psychosocial modalities, such as CBT, supportive therapy, or contingency management, have some evidence to support their efficacy in patients with substance use disorders [98; 106].

FACTORS IMPACTING RECOVERY

Stigma

Although substance use disorders affect millions of persons in the United States every year, stigma and shame surrounding these disorders remains. Although it is clear that substance use disorders are complex mental disorders, many continue to view it as a result of moral weakness and flawed character [107]. Experiences of this stigma, especially if expressed by a healthcare professional, can impede patients from seeking help or adhering to treatment.

Trauma

Various studies have found a disproportionately higher number of abuse, neglect, or trauma histories in patients with substance use disorders than in the general population [108; 109; 110; 111; 112]. Furthermore, substance abuse increases the likelihood of victimization, which can further promulgate the cycle of coping with trauma-related stress and self-medicating with addictive substances [113; 114; 115; 116; 117].

Some experts have asserted that traditional models of addiction recovery and relapse prevention do not consider the significant role that unresolved trauma can play in an addicted individual's attempt at recovery [118]. It is possible that traditional approaches tend to marginalize women more than their male counterparts and fail to sufficiently address the role that trauma has played in the development and maintenance of substance use disorder. An integrated, more holistic approach is needed to promote long-term recovery and prevent relapse [119].

Social Determinants of Health

Social determinants of health are the conditions in the environments where people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks. They can have a major impact on substance use disorder treatment and recovery. Examples of social determinants of health include [120]:

- Safe housing, transportation, and neighborhoods
- Racism, discrimination, and violence
- Education, job opportunities, and income
- Access to nutritious foods and physical activity opportunities
- Polluted air and water
- Language and literacy skills

Social determinants of health also contribute to wide health disparities and inequities. For example, people who lack reliable transportation are less likely to attend follow-up appointments or 12-step meetings, which raises the risk of relapse and treatment nonadherence [120].

LEGAL AND ETHICAL ISSUES IN THE TREATMENT OF SUBSTANCE USE DISORDERS

Federal statutes, regulations, and guidelines govern medications for opioid addiction. The SAMHSA's Division of Pharmacologic Therapies, part of SAMHSA's Center for Substance Abuse Treatment, manages the day-to-day oversight activities required to implement federal regulations surrounding the use medications approved by the FDA, such as methadone and buprenorphine for the treatment of opioid use disorder for practitioners and opioid treatment programs [121]. Some medications used to treat substance use disorder are controlled substances governed by the Controlled Substances Act.

Section 1262 of the Consolidated Appropriations Act of 2023 (also known as Omnibus bill), removes the federal requirement for practitioners to submit a Notice of Intent (i.e., have a DATA or X-waiver) to prescribe medications, like buprenorphine, for the treatment of opioid use disorder. All practitioners who have a current Drug Enforcement Administration (DEA) registration that includes Schedule III authority may now prescribe buprenorphine for opioid use disorder in their practice if permitted by applicable state law. This section also removes other federal requirements associated with the waiver, such as discipline restrictions, patient limits, and certification related to provision of counseling. Separately, section 1263 of the Consolidated Appropriations Act requires new or renewing DEA registrants, starting June 27, 2023, upon submission of their application, to have at least one of the following [122]:

- A total of eight hours of training from certain organizations on opioid or other substance use disorders for practitioners renewing or newly applying for a registration from the DEA to prescribe any Schedule II-V controlled medications
- Board certification in addiction medicine or addiction psychiatry from the American Board of Medical Specialties, American Board of Addiction Medicine, or the American Osteopathic Association
- Graduation within five years and status in good standing from medical, dental medicine, advanced practice nursing, or physician assistant school in the United States that included successful completion of an opioid or other substance use disorder curriculum of at least eight hours
- For dentists, the training may also include the safe pharmacologic management of dental pain and screening, brief intervention, and referral for appropriate treatment of patients with or at risk of developing opioid and other substance use disorders

Key ethical issues to consider when caring for patients with substance use disorders include informed consent, confidentiality, autonomy, competence, access to services, and explicit and implicit bias.

PAIN MANAGEMENT AND SUBSTANCE MISUSE

Persistent pain has been reported to affect one in three adults in the United States [123]. As such, a significant portion of persons with substance use disorders will have comorbid and sometimes chronic pain. There is no adequately validated instrument to differentiate pain patients who are at risk of dependence from those who are not. Research suggests that patients, even those with alcohol use disorder, with no history of opioid dependence are not at heightened risk of becoming addicted with short-term opioid exposure. However, those with a positive history of dependence would benefit from active recovery efforts while receiving such medications.

Despite the rise in prescription opioid analgesic use and misuse, definitive data on the rate of dependence among patients administered opioids for acute pain does not yet exist. There is, however, agreement on how to minimize the risk of iatrogenic dependence. These steps include screening for risk potential based on a family history of substance abuse and the exploration of different delivery systems that adequately treat pain but minimize abuse potential. Although a pattern of aberrant behavior may be grounds for caution, a history of opioid misuse does not necessarily preclude a patient from successful treatment with an opioid. Screening for psychologic disorders is also advisable, including psychosomatic causes of pain.

PAIN MANAGEMENT APPROACHES

Healthcare professionals should know the best clinical practices in opioid prescribing, including the associated risks of opioids, approaches to the assessment of pain and function, and pain management modalities. Pharmacologic and nonpharmacologic approaches should be used on the basis of current knowledge in the evidence base or best clinical practices. Patients with moderate-to-severe chronic pain who have been assessed and treated, over a period of time, with non-opioid therapy or nonpharmacologic pain therapy without adequate pain relief, are considered to be candidates for a trial of opioid therapy [124; 125; 127]. Initial treatment should always be considered individually determined and as a trial of therapy, not a definitive course of treatment [126].

The Centers for Disease Control and Prevention (CDC) originally published *Guideline for Prescribing Opioids for Chronic Pain—United States, 2016* in an effort to address an ongoing crisis of prescription opioid misuse, abuse, and overdose [125]. While these guidelines were based on the best available evidence at the time, there was some criticism that they were too focused on limiting opioid prescriptions—to the point of patients and prescribers complaining of stigma and reduced access to needed opioid analgesics. In response to this and to the availability of new evidence, the CDC published updates to the guideline in 2022 [127]. The updated clinical practice guideline is intended to achieve improved communication between clinicians and patients about the risks and benefits of pain treatment, including opioid therapy for pain; improved safety and effectiveness for pain treatment, resulting in improved function and quality of life for patients experiencing pain; and a reduction in the risks associated with long-term opioid therapy, including opioid use disorder, overdose, and death [127].

The 2022 clinical practice guideline includes 12 recommendations for clinicians who are prescribing opioids for outpatients 18 years of age or older with acute (duration <1 month) pain, subacute (duration of 1 to 3 months) pain, or chronic (duration of >3 months) pain outside of sickle cell disease related pain management, cancer pain treatment, palliative care, and end-of-life care. These recommendations are graded according to applicability and strength of the supporting evidence [127].

Acute Pain

Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids in a quantity no greater than that needed for the expected duration of severe pain. In most cases, three days or less will be sufficient; more than seven days will rarely be needed [125; 127]. However, it may be necessary to prescribe for longer periods in patients with acute severe pain. Approximately half of all states have passed legislation limiting initial opioid prescriptions for acute pain to a seven-day supply or less, and many insurers, pharmacy benefit managers, and pharmacies have enacted similar policies [127].

With postoperative, acute, or intermittent pain, analgesia often requires frequent titration, and the two- to four-hour analgesic duration with short-acting hydrocodone, morphine, and oxycodone is more effective than extended-release formulations. Short-acting opioids are also recommended in patients who are medically unstable or with highly variable pain intensity [128; 129; 130].

Chronic Pain

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

Implantable intrathecal opioid infusion and/or spinal cord stimulation may be options for severe, intractable pain. Both options require that devices or ports be implanted, with associated risks. With intrathecal opioid infusion, the ability to deliver the drug directly into the spine provides pain relief with significantly smaller opioid doses, which can help to minimize side effects (e.g., drowsiness, dizziness, dry mouth, nausea, vomiting, and constipation) that can accompany systemic pain medications that might be delivered orally, transdermally, or through an IV [131]. However, use of opioid infusion has traditionally been limited to cancer pain. With spinal cord stimulation therapy, the most challenging aspect is patient selection. In order for patients to be considered for spinal cord stimulation, other options should have been ineffective or be contraindicated. Spinal cord stimulation is indicated for severe neuropathic pain persisting at least six months.

If opioids are used, they should be combined with nonpharmacologic therapy and non-opioid pharmacologic therapy, as appropriate. Clinicians should consider opioid therapy only if expected benefits for pain and function are anticipated to outweigh risks to the patient [125; 127].

Opioid therapy for chronic pain should be presented as a trial for a pre-defined period (e.g., ≤30 days). The goals of treatment should be established with all patients prior to the initiation of opioid therapy, including reasonable improvements in pain, function, depression, anxiety, and avoidance of unnecessary or excessive medication use [125; 127; 132]. The treatment plan should describe therapy selection, measures of progress, and other diagnostic evaluations, consultations, referrals, and therapies.

In patients who are opioid-naïve, start at the lowest possible dose and titrate to effect. Dosages for patients who are opioid-tolerant should always be individualized and titrated by efficacy and tolerability [125; 127; 132]. When starting opioid therapy for chronic pain, clinicians should prescribe short-acting instead of extended-release/long-acting opioid formulations [125; 127].

The need for frequent progress and benefit/risk assessments during the trial should be included in patient education. Patients should also have full knowledge of the warning signs and symptoms of respiratory depression. Prescribers should carefully reassess evidence of benefits and risks when increasing the dosage to ≥50 mg morphine milligram equivalents (MME) per day. In its 2016 guideline, the CDC recommended that decisions to titrate dosage to ≥90 mg MME/day should be avoided or carefully justified [125; 133]. This recommendation does not appear in the 2022 revision [127].

Prescribers should be knowledgeable of federal and state opioid prescribing regulations. Issues of equianalgesic dosing, close patient monitoring during all dose changes, and cross-tolerance with opioid conversion should be considered. If necessary, treatment may be augmented, with preference for nonopioid and immediate-release opioids over long-acting/extended-release opioids. Taper opioid dose when no longer needed [134].

Palliative Care and Pain at the End of Life

Unrelieved pain is the greatest fear among people with a life-limiting disease, and the need for an increased understanding of effective pain management is well-documented [135]. Although experts have noted that 75% to 90% of end-of-life pain can be managed effectively, rates of pain are high, even among people receiving palliative care [135; 136; 137; 138].

The inadequate management of pain is the result of several factors related to both patients and clinicians. In a survey of oncologists, patient reluctance to take opioids or to report pain were two of the most important barriers to effective pain relief [139]. This reluctance is related to a variety of attitudes and beliefs [135; 139]:

- Fear of addiction to opioids
- Worry that if pain is treated early, there will be no options for treatment of future pain
- Anxiety about unpleasant side effects from pain medications

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

Education and open communication are the keys to overcoming these barriers. Every member of the healthcare team should reinforce accurate information about pain management with patients and families. The clinician should initiate conversations about pain management, especially regarding the use of opioids, as few patients will raise the issue themselves or even express their concerns unless they are specifically asked [140]. It is important to acknowledge patients' fears individually and provide information to help them differentiate fact from fiction. For example, when discussing opioids with a patient who fears addiction, the clinician should explain that the risk of addiction is low [135]. It is also helpful to note the difference between addiction and physical dependence.

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

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

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

Clinicians' attitudes, beliefs, and experiences also influence pain management, with addiction, tolerance, side effects, and regulations being the most important concerns [135; 137; 139; 141]. A lack of appropriate education and training in the assessment and management of pain has been noted to be a substantial contributor to ineffective pain management [139; 141]. As a result, many clinicians, especially primary care physicians, do not feel confident about their ability to manage pain in their patients [139; 141].

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

Strong opioids are used for severe pain at the end of life [136; 137]. Morphine, buprenorphine, oxycodone, hydromorphone, fentanyl, and methadone are the most widely used in the United States [142]. Unlike nonopioids, opioids do not have a ceiling effect, and the dose can be titrated until pain is relieved or side effects become unmanageable. Patients who are opioid-naïve or who have been receiving low doses of a weak opioid, the initial dose should be low, and, if pain persists, the dose may be titrated up daily until pain is controlled.

More than one route of opioid administration will be needed by many patients during end-of-life care, but in general, opioids should be given orally, as this route is the most convenient and least expensive. The transdermal route is preferred to the parenteral route, although dosing with a transdermal patch is less flexible and so may not be appropriate for patients with unstable pain [137]. Intramuscular injections should be avoided because injections are painful, drug absorption is unreliable, and the time to peak concentration is long [137].

CREATING A TREATMENT PLAN AND ASSESSMENT OF ADDICTION RISK

Information obtained by patient history, physical examination, and interview, from family members, a spouse, or state prescription drug monitoring program (PDMP), and from the use of screening and assessment tools can help the clinician to stratify the patient according to level of risk for developing problematic opioid behavioral responses (***Table 3***) [143; 144]. Low-risk patients receive the standard level of monitoring, vigilance, and care. Moderate-risk patients should be considered for an additional level of monitoring and provider contact, and high-risk patients are likely to require intensive and structured monitoring and follow-up contact, additional consultation with psychiatric and addiction medicine specialists, and limited supplies of short-acting opioid formulations [125; 127; 145].

Before deciding to prescribe an opioid analgesic, clinicians should perform and document a detailed patient assessment that includes [132]:

- Pain indications for opioid therapy
- Nature and intensity of pain
- Past and current pain treatments and patient response
- Comorbid conditions
- Pain impact on physical and psychologic function
- Social support, housing, and employment
- Home environment (i.e., stressful or supportive)
- Pain impact on sleep, mood, work, relationships, leisure, and substance use
- Patient history of physical, emotional, or sexual abuse

If substance abuse is active, in remission, or in the patient's history, consult an addiction specialist before starting opioids [132]. In active substance abuse, do not prescribe opioids until the patient is engaged in treatment/recovery program or other arrangement made, such as addiction professional co-management and additional monitoring. When considering an opioid analgesic (particularly those that are extended-release or long-acting), one must always weigh the benefits against the risks of overdose, abuse, addiction, physical dependence and

RISK STRATIFICATION FOR PATIENTS PRESCRIBED OPIOIDS
Low Risk
Definable physical pathology with objective signs and reliable symptoms
Clinical correlation with diagnostic testing, including MRI, physical examination, and interventional diagnostic techniques
With or without mild psychologic comorbidity
With or without minor medical comorbidity
No or well-defined and controlled personal or family history of alcoholism or substance abuse
Age 45 years or older
High levels of pain acceptance and active coping strategies
High motivation and willingness to participate in multimodal therapy and attempting to function at normal levels
Medium Risk
Significant pain problems with objective signs and symptoms confirmed by radiologic evaluation, physical examination, or diagnostic interventions
Moderate psychologic problems, well controlled by therapy
Moderate coexisting medical disorders that are well controlled by medical therapy and are not affected by chronic opioid therapy (e.g., central sleep apnea)
Develops mild tolerance but not hyperalgesia without physical dependence or addiction
History of personal or family history of alcoholism or substance abuse
Pain involving more than three regions of the body
Defined pathology with moderate levels of pain acceptance and coping strategies
Willing to participate in multimodal therapy, attempting to function in normal daily life
High Risk
Widespread pain without objective signs and symptoms
Pain involving more than three regions of the body
Aberrant drug-related behavior
History of alcoholism or drug misuse, abuse, addiction, diversion, dependency, tolerance, or hyperalgesia
Major psychologic disorders
Age younger than 45 years
HIV-related pain
High levels of pain exacerbation and low levels of coping strategies
Unwilling to participate in multimodal therapy, not functioning close to a near normal lifestyle
HIV = human immunodeficiency syndrome, MRI = magnetic resonance imaging.
Source: [143; 144] *Table 3*

tolerance, adverse drug interactions, and accidental exposure by children [125; 127; 134].

Screening and assessment tools can help guide patient stratification according to risk level and inform the appropriate degree of structure and monitoring in the treatment plan. It should be noted that despite widespread endorsement of screening tools used to help determine patient risk level, most tools have not been extensively evaluated, validated, or compared to each other, and evidence of their reliability is poor [143; 144].

Risk Assessment Tools

Opioid Risk Tool (ORT)

The Opioid Risk Tool (ORT) is a five-item, patient-administered assessment to help predict aberrant drug-related behavior. The ORT is also used to establish patient risk level through categorization into low, medium, or high levels of risk for aberrant drug-related behaviors based on responses to questions of previous alcohol/drug abuse, psychologic disorders, and other risk factors [146].

Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)

The Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) is a patient-administered, 24-item screen with questions addressing history of alcohol/substance use, psychologic status, mood, cravings, and stress. Like the ORT, the SOAPP-R helps assess risk level of aberrant drug-related behaviors and the appropriate extent of monitoring [146; 147].

Screening Instrument or Substance Abuse Potential (SISAP)

The Screening Instrument or Substance Abuse Potential (SISAP) tool is a self-administered, five-item questionnaire addressing history developed used to predict the risk of opioid misuse. The SISAP is used to identify patients with a history of alcohol/substance abuse and improve pain management by facilitating focus on the appropriate use of opioid analgesics and therapeutic outcomes in the majority of patients who are not at risk of opioid abuse, while carefully monitoring those who may be at greater risk [146].

CAGE and CAGE-AID

The original CAGE (Cut down, Annoyed, Guilty, and Eye-opener) Questionnaire consisted of four questions designed to help clinicians determine the likelihood that a patient was misusing or abusing alcohol. These same four questions were modified to create the CAGE-AID (adapted to include drugs), revised to assess the likelihood of current substance abuse [148].

Diagnosis, Intractability, Risk, and Efficacy (DIRE) Score

The Diagnosis, Intractability, Risk, and Efficacy (DIRE) risk assessment score is a clinician-rated questionnaire that is used to predict patient compliance with long-term opioid therapy [146; 149]. Patients scoring lower on the DIRE tool are poor candidates for long-term opioid analgesia.

Considerations for Pain Management in Patients with Comorbid Opioid Use Disorder

Although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. Clinicians should use nonpharmacologic and nonopioid pharmacologic pain treatments as appropriate to provide optimal pain management [150]. For patients with pain who have an active opioid use disorder but are not in treatment, clinicians should consider buprenorphine or methadone treatment for opioid use disorder, which can also help with concurrent management of pain [150]. For patients who are treated with buprenorphine for opioid use disorder and experience acute pain, clinicians can consider temporarily increasing the buprenorphine dosing frequency (e.g., to twice a day) to help manage pain, given the duration of effects of buprenorphine is shorter for pain than for suppression of withdrawal [150; 151]. For severe acute pain (e.g., from trauma or unplanned major surgery) in patients receiving buprenorphine for opioid use disorder, clinicians can consider additional as-needed doses of buprenorphine. In supervised settings, adding a short-acting full agonist opioid to the patient's regular dosage of buprenorphine can be considered without discontinuing the patient's regular buprenorphine dosage; however, if a decision is made to discontinue buprenorphine to allow for more mu-opioid receptor availability, patients should be monitored closely because high doses of a full agonist opioid might be required, potentially leading to oversedation and respiratory depression as buprenorphine's partial agonist effect lessens. For patients receiving naltrexone for opioid use disorder, short-term use of higher-potency nonopioid analgesics (e.g., NSAIDs) can be considered to manage severe acute pain. Patients receiving methadone for opioid use disorder who require additional opioids as treatment for severe acute pain management should be carefully monitored, and when feasible should optimally be treated by a clinician experienced in the treatment of pain in consultation with their opioid treatment program [150]. The ASAM *National Practice Guideline for the Treatment of Opioid Use Disorder (2020 Focused Update)* provides additional recommendations for the management of patients receiving medications for opioid use disorder who have planned surgeries for which nonopioid therapies are not anticipated to provide sufficient pain relief [150].

Informed Consent and Treatment Agreements

The initial opioid prescription is preceded by a written informed consent or "treatment agreement" [132]. This agreement should address potential side effects, tolerance and/or physical dependence, drug interactions, motor skill impairment, limited evidence of long-term benefit, misuse, dependence, addiction, and overdose. Informed consent documents should include information regarding the risk/benefit profile for the drug(s) being prescribed. The prescribing policies should be clearly delineated, including the number/frequency of refills, early refills, and procedures for lost or stolen medications.

The treatment agreement also outlines joint physician and patient responsibilities. The patient agrees to using medications safely, refraining from "doctor shopping," and consenting to routine urine drug testing (UDT). The prescriber's responsibility is to address unforeseen problems and prescribe scheduled refills. Reasons for opioid therapy change or discontinuation should be listed. Agreements can also include sections related to follow-up visits, monitoring, and safe storage and disposal of unused drugs.

Periodic Review and Monitoring

When implementing a chronic pain treatment plan that involves the use of opioids, the patient should be frequently reassessed for changes in pain origin, health, and function [132]. This can include input from family members and/or the state PDMP. During the initiation phase and during any changes to the dosage or agent used, patient contact should be increased. At every visit, chronic opioid response may be monitored according to the "5 A's" [132; 152]:

- Analgesia
- Activities of daily living
- Adverse or side effects
- Aberrant drug-related behaviors
- Affect (i.e., patient mood)

Signs and symptoms that, if present, may suggest a problematic response to the opioid and interference with the goal of functional improvement include [153; 154]:

- Excessive sleeping or days and nights turned around
- Diminished appetite
- Short attention span or inability to concentrate
- Mood volatility, especially irritability
- Lack of involvement with others
- Impaired functioning due to drug effects
- Use of the opioid to regress instead of re-engaging in life
- Lack of attention to hygiene and appearance

The decision to continue, change, or terminate opioid therapy is based on progress toward treatment objectives and absence of adverse effects and risks of overdose or diversion [132]. Satisfactory therapy is indicated by improvements in pain, function, and quality of life. Brief assessment tools to assess pain and function may be useful, as may UDTs. Treatment plans may include periodic pill counts to confirm adherence and minimize diversion.

Involvement of Family

Family members of the patient can provide the clinician with valuable information that better informs decision making regarding continuing opioid therapy. Family members can observe whether a patient is losing control of his or her life or becoming less functional or more depressed during the course of opioid therapy. They can also provide input regarding positive or negative changes in patient function, attitude, and level of comfort. The following questions can be asked of family members or a spouse to help clarify whether the patient's response to opioid therapy is favorable or unfavorable [153; 154]:

- Is the person's day centered around taking the opioid medication? Response can help clarify long-term risks and benefits of the medication and identify other treatment options.
- Does the person take pain medication only on occasion, perhaps three or four times per week? If yes, the likelihood of addiction is low.
- Have there been any other substance (alcohol or drug) abuse problems in the person's life? An affirmative response should be taken into consideration when prescribing.
- Does the person in pain spend most of the day resting, avoiding activity, or feeling depressed? If so, this suggests the pain medication is failing to promote rehabilitation. Daily activity is essential, and the patient may be considered for enrollment in a graduated exercise program.
- Is the person in pain able to function (e.g., work, do household chores, play) with pain medication in a way that is clearly better than without? If yes, this suggests the pain medication is contributing to wellness.

Assessment Tools

VIGIL is the acronym for a five-step risk management strategy designed to empower clinicians to appropriately prescribe opioids for pain by reducing regulatory concerns and to give pharmacists a framework for resolving ambiguous opioid analgesic prescriptions in a manner that preserves legitimate patient need while potentially deterring diverters. The components of VIGIL are:

- Verification: Is this a responsible opioid user?
- Identification: Is the identity of this patient verifiable?
- Generalization: Do we agree on mutual responsibilities and expectations?
- Interpretation: Do I feel comfortable allowing this person to have controlled substances?
- Legalization: Am I acting legally and responsibly?

The foundation of VIGIL is a collaborative physician/pharmacist relationship [155].

The Current Opioid Misuse Measure (COMM) is a 17-item patient self-report assessment designed to help clinicians identify misuse or abuse in patients being treated for chronic pain. Unlike the ORT and the SOAPP-R, the COMM identifies aberrant behaviors associated with opioid misuse in patients already receiving long-term opioid therapy [145]. Sample questions include: In the past 30 days, how often have you had to take more of your medication than prescribed? In the past 30 days, how much of your time was spent thinking about opioid medications (e.g., having enough, taking them, dosing schedule)?

Guidelines by the CDC, the Federation of State Medical Boards (FSMB), and the Joint Commission stress the importance of documentation from both a healthcare quality and medicolegal perspective. Research has found widespread deficits in chart notes and progress documentation with patients with chronic pain receiving opioid therapy, and the Pain Assessment and Documentation Tool (PADT) was designed to address these shortcomings [156]. The PADT is a clinician-directed interview, with most sections (e.g., analgesia, activities of daily living, adverse events) consisting of questions asked of the patient. However, the potential aberrant drug-related behavior section must be completed by the physician based on his or her observations of the patient.

The Brief Intervention Tool is a 26-item, "yes-no," patient-administered questionnaire used to identify early signs of opioid abuse or addiction. The items assess the extent of problems related to drug use in several areas, including drug use-related functional impairment [157].

PATIENT RISK LEVEL AND FREQUENCY OF MONITORING			
Monitoring Tool	**Patient Risk Level**		
	Low	**Medium**	**High**
Urine drug test	Every 1 to 2 years	Every 6 to 12 months	Every 3 to 6 months
State prescription drug monitoring program	Twice per year	Three times per year	Four times per year
Source: [158]			*Table 4*

Urine Drug Tests

UDTs may be used to monitor adherence to the prescribed treatment plan and to detect unsanctioned drug use. They should be used more often in patients receiving addiction therapy, but clinical judgment is the ultimate guide to testing frequency (***Table 4***) [158]. The CDC recommends clinicians should use UDT before starting opioid therapy and consider UDT at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs [125; 127]. However, this recommendation was based on low-quality evidence that indicates little confidence in the effect estimate.

Initially, testing involves the use of class-specific immunoassay drug panels [132]. If necessary, this may be followed with gas chromatography/mass spectrometry for specific drug or metabolite detection. It is important that testing identifies the specific drug rather than the drug class, and the prescribed opioid should be included in the screen. Any abnormalities should be confirmed with a laboratory toxicologist or clinical pathologist. Immunoassay may be used point-of-care for "on-the-spot" therapy changes, but the high error rate prevents its use in major clinical decisions except with liquid chromatography coupled to tandem mass spectrometry confirmation.

Urine test results suggesting opioid misuse should be discussed with the patient using a positive, supportive approach. The test results and the patient discussion should be documented.

Concurrent Use of Benzodiazepines

In 2019, 16% of persons who died of an opioid overdose also tested positive for benzodiazepines, a class of sedative medication commonly prescribed for anxiety, insomnia, panic attack, and muscle spasm [159]. Benzodiazepines work by raising the level of GABA in the brain. Common formulations include diazepam, alprazolam, and clonazepam. Combining benzodiazepines with opioids is unsafe because both classes of drug cause central nervous system depression and sedation and can decrease respiratory drive—the usual cause of overdose fatality. Both classes have the potential for drug dependence and addiction.

The CDC recommends that healthcare providers use particular caution prescribing benzodiazepines concurrently with opioids [125; 127]. If a benzodiazepine is to be discontinued, the clinician should taper the medication gradually, because abrupt withdrawal can lead to rebound anxiety and complications such as hallucinations, seizures, delirium tremens, and, in rare instances, death. A commonly used tapering schedule is a reduction of the benzodiazepine dose by 25% every one to two weeks [125; 127].

Consultation and Referral

It is important to seek consultation or patient referral when input or care from a pain, psychiatry, addiction, or mental health specialist is necessary. Clinicians who prescribe opioids should become familiar with opioid addiction treatment options (including licensed opioid treatment programs for methadone and office-based opioid treatment for buprenorphine) if referral is needed [132].

Ideally, providers should be able to refer patients with active substance abuse who require pain treatment to an addiction professional or specialized program. In reality, these specialized resources are scarce or non-existent in many areas [132]. Therefore, each provider will need to decide whether the risks of continuing opioid treatment while a patient is using illicit drugs outweigh the benefits to the patient in terms of pain control and improved function [160].

Medical Records

As noted, documentation is a necessary aspect of all patient care, but it is of particular importance when opioid prescribing is involved. All clinicians should maintain accurate, complete, and up-to-date medical records, including all written or telephoned prescription orders for opioid analgesics and other controlled substances, all written instructions to the patient for medication use, and the name, telephone number, and address of the patient's pharmacy [132]. Good medical records demonstrate that a service was provided to the patient and that the service was medically necessary. Regardless of the treatment outcome, thorough medical records protect the prescriber.

Patient Education on the Use and Disposal of Opioids

Patients and caregivers should be counseled regarding the safe use and disposal of opioids. As part of its mandatory Risk Evaluation and Mitigation Strategy (REMS) for extended-release/long-acting opioids, the FDA has developed a patient counseling document with information on the patient's specific medications, instructions for emergency situations and incomplete pain control, and warnings not to share medications or take them unprescribed [134]. A copy of this form may be accessed online at https://www.fda.gov/media/114694/download.

When prescribing opioids, clinicians should provide patients with the following information [134]:

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

There are no universal recommendations for the proper disposal of unused opioids, and patients are rarely advised of what to do with unused or expired medications [161]. According to the FDA, most medications that are no longer necessary or have expired should be removed from their containers, mixed with undesirable substances (e.g., cat litter, used coffee grounds), and put into an impermeable, nondescript container (e.g., disposable container with a lid or a sealed bag) before throwing in the trash [162]. Any personal information should be obscured or destroyed. The FDA recommends that certain medications, including oxycodone/acetaminophen (Percocet), oxycodone (OxyContin tablets), and transdermal fentanyl (Duragesic Transdermal System), be flushed down the toilet instead of thrown in the trash [162; 163]. The FDA provides a free toolkit of materials (e.g., social media images, fact sheets, posters) to raise awareness of the serious dangers of keeping unused opioid pain medicines in the home and with information about safe disposal of these medicines. The Remove the Risk Outreach toolkit is updated regularly and can be found at https://www.fda.gov/drugs/ensuring-safe-use-medicine/safe-opioid-disposal-remove-risk-outreach-toolkit [163]. Patients should be advised to flush prescription drugs down the toilet only if the label or accompanying patient information specifically instructs doing so.

The American College of Preventive Medicine has established best practices to avoid diversion of unused drugs and educate patients regarding drug disposal [161]:

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

Discontinuing Opioid Therapy

The decision to continue or end opioid prescribing should be based on a physician-patient discussion of the anticipated benefits and risks. An opioid should be discontinued with resolution of the pain condition, intolerable side effects, inadequate analgesia, lack of improvement in quality of life despite dose titration, deteriorating function, or significant aberrant medication use [125; 127; 132].

Clinicians should provide patients physically dependent on opioids with a safely structured tapering protocol. Withdrawal is managed by the prescribing physician or referral to an addiction specialist. Patients should be reassured that opioid discontinuation is not the end of treatment; continuation of pain management will be undertaken with other modalities through direct care or referral.

As a side note, cannabis use by patients with chronic pain receiving opioid therapy has traditionally been viewed as a treatment agreement violation that is grounds for termination of opioid therapy. However, some now argue against cannabis use as a rationale for termination or substantial treatment and monitoring changes, especially considering the increasing legalization of medical use at the state level [160].

Considerations for Non-English-Proficient Patients

For patients who are not proficient in English, it is important that information regarding the risks associated with the use of opioids and available resources be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more

than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter. In any case in which information regarding treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered. Print materials are also available in many languages, and these should be offered whenever necessary.

IDENTIFICATION OF DRUG DIVERSION/SEEKING BEHAVIORS

Research has more closely defined the location of prescribed opioid diversion into illicit use in the supply chain from the manufacturer to the distributor, retailer, and the end user (the pain patient). This information carries with it substantial public policy and regulatory implications. The 2021 National Survey on Drug Use and Health asked non-medical users of prescription opioids how they obtained their most recently used drugs [2]. Among persons 12 years of age or older, 39.3% obtained their prescription opioids through a prescription from one doctor (vs. 34.7% in 2019), 33.9% got them from a friend or relative for free, 7.9% bought from a drug dealer or other stranger, and 7.3% bought them from a friend or relative [2]. Less frequent sources included stealing from a friend or relative (3.7%); multiple doctors (3.2%); and theft from a doctor's office, clinic, hospital, or pharmacy (0.7%) (vs. 0.2% in 2009–2010) [2].

As discussed, UDTs can give insight into patients who are misusing opioids. A random sample of UDT results from 800 patients treated for pain at a Veterans Affairs facility found that 25.2% were negative for the prescribed opioid while 19.5% were positive for an illicit drug/unreported opioid [164]. Negative UDT results for the prescribed opioid do not necessarily indicate diversion, but may indicate the patient halted his/her use due to side effects, lack of efficacy, or pain remission. The concern arises over the increasingly stringent climate surrounding clinical decision-making regarding aberrant UDT results and that a negative result for the prescribed opioid or a positive UDT may serve as the pretense to terminate a patient rather than guide him/her into addiction treatment or an alternative pain management program [165].

In addition to aberrant urine screens, there are certain behaviors that are suggestive of an emerging opioid use disorder. The most suggestive behaviors are [160; 166; 167]:

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

Behaviors with a lower level of evidence for their association with opioid misuse include [160; 166; 167]:

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

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Institute for Clinical Systems Improvement recommends considering screening patients for substance use disorders when there is an unclear etiology of pain.

(https://www.icsi.org/wp-content/uploads/2019/10/Pain-Interactive-7th-V2-Ed-8.17.pdf. Last accessed April 27, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

INTERVENTIONS FOR SUSPECTED OR KNOWN ADDICTION OR DRUG DIVERSION

There are a number of actions that prescribers and dispensers can take to prevent or intervene in cases of drug diversion. These actions can be generally categorized based on the various mechanisms of drug diversion.

Prevention is the best approach to addressing drug diversion. As noted, the most common source of nonmedical use of prescribed opioids is from a family member or friend, through sharing, buying, or stealing. To avoid drug sharing among patients, healthcare professionals should educate patients on the dangers of sharing opioids and stress that "doing prescription drugs" is the same as "using street drugs" [161]. In addition, patients should be aware of the many options available to treat chronic pain aside from opioids. To prevent theft, patients should be advised to keep medications in a private place and to refrain from telling others about the medications being used.

Communication among providers and pharmacies can help to avoid inappropriate attainment of prescription drugs through "doctor shopping." Prescribers should keep complete and up-to-date records for all controlled substance prescribing. When possible, electronic medical records should be integrated between pharmacies, hospitals, and managed care organizations [161]. If available, it is also best practice to periodically request a report from the state's prescription reporting program to evaluate the prescribing of opioids to your patients by other providers [161].

When dealing with patients suspected of drug seeking/diversion, first inquire about prescription, over-the-counter, and illicit drug use and perform a thorough examination [161]. Pill counting and/or UDT may be necessary to investigate possible drug misuse. Photo identification or other form of identification and social security number may be required prior to dispensing the drug, with proof of identity documented fully. If a patient is displaying suspicious behaviors, consider prescribing for limited quantities.

If a patient is found to be abusing prescribed opioids, this is considered a violation of the treatment agreement and the clinician must make the decision whether or not to continue the therapeutic relationship. If the relationship is terminated, it must be done ethically and legally. The most significant issue is the risk of patient abandonment, which is defined as ending a relationship with a patient without consideration of continuity of care and without providing notice to the patient. The American Medical Association Code of Ethics states that physicians have an obligation to support continuity of care for their patients. While physicians have the option of withdrawing from a case, they should notify the patient (or authorized decision maker) long enough in advance to permit the patient to secure another physician and facilitate transfer of care when appropriate [168]. Patients may also be given resources and/or recommendations to help them locate a new clinician.

Patients with chronic pain found to have an ongoing substance abuse problem or addiction should be referred to a pain specialist for continued treatment. Theft or loss of controlled substances is reported to the DEA. If drug diversion has occurred, the activity should be documented and a report to law enforcement should be made [169].

COMPLIANCE WITH STATE AND FEDERAL LAWS

In response to the rising incidence in prescription opioid abuse, addiction, diversion, and overdose since the late 1990s, the FDA has mandated opioid-specific REMS to reduce the potential negative patient and societal effects of prescribed opioids. Other elements of opioid risk mitigation include FDA partnering with other governmental agencies, state professional licensing boards, and societies of healthcare professionals to help improve prescriber knowledge of appropriate and safe opioid prescribing and safe home storage and disposal of unused medication [153].

Several regulations and programs at the state level have been enacted in an effort to reduce prescription opioid abuse, diversion, and overdose, including [170]:

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

Controlled Substances Laws/Rules

The DEA is responsible for formulating federal standards for the handling of controlled substances. In 2011, the DEA began requiring every state to implement electronic databases that track prescribing habits, referred to as PDMPs. Specific policies regarding controlled substances are administered at the state level [171].

According to the DEA, drugs, substances, and certain chemicals used to make drugs are classified into five distinct categories or schedules depending upon the drug's acceptable medical use and the drug's abuse or dependency potential [172]. The abuse rate is a determinate factor in the scheduling of the drug; for example, Schedule I drugs are considered the most dangerous class of drugs with a high potential for abuse and potentially severe psychologic and/or physical dependence.

State-Specific Laws and Rules

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

CONCLUSION

Substance use disorders are associated with serious morbidity and mortality, and advances in the understanding of these disorders have led to the development of effective treatments. More recently, the abuse of prescription opioids has become considerably more widespread, fueled in part by the availability of such drugs over the Internet. Medical, mental health, and other healthcare professionals in a variety of settings may encounter patients with comorbid substance use disorders and pain. The knowledge gained from the contents of this course can greatly assist the healthcare professional in identifying, treating, and providing an appropriate referral to patients with substance use disorders while also addressing pain management needs.

Customer Information/Answer Sheet/Evaluation insert located between pages 60–61.

TEST QUESTIONS
#95300 SUBSTANCE USE DISORDERS AND PAIN MANAGEMENT: MATE ACT TRAINING

This is an open book test. Please record your responses on the Answer Sheet.
A passing grade of at least 80% must be achieved in order to receive credit for this course.

This 8 Credit activity must be completed by April 30, 2026.

1. Which of the following is a risk factor for the development of a substance use disorder?
- A) *Genetic predisposition*
- B) *Adverse childhood experiences*
- C) *Children with conduct problems*
- D) *All of the above*

2. All of the following are diagnostic criteria for substance use disorders, EXCEPT:
- A) *Tolerance*
- B) *Withdrawal*
- C) *Recreational use*
- D) *Persistent desire or unsuccessful efforts to cut down or control use*

3. Which of the following statements regarding contingency management interventions is TRUE?
- A) *There is little evidence that substance use is sensitive to the application of contingencies.*
- B) *Contrived contingencies are less likely to result in relapse to drug use following removal of the reinforcer.*
- C) *Naturalistic contingencies are less likely to maintain the initial gains made by the patient and to facilitate the sustained change of behavior over time.*
- D) *The goal is to increase the opportunity cost of substance use by arranging an environment where drug use results in the forfeiture of a predetermined item or privilege.*

4. Which of the following is NOT a primary area addressed by coping and social skill training (CSST)?
- A) *Solitude training*
- B) *Cognitive and affective regulation*
- C) *Coping skills to manage stressful life events*
- D) *Coping skills when substances or substance-related cues are encountered*

5. Which of the following is a common side effect associated with naltrexone?
- A) *Dizziness*
- B) *Weight gain*
- C) *Difficulty breathing*
- D) *Decreased interest in sex*

6. Which of the following drugs is considered the criterion standard in reversing respiratory depression and coma in acute opioid overdose?
- A) *LAAM*
- B) *Naloxone*
- C) *Methadone*
- D) *Buprenorphine*

7. Buprenorphine is most effective at a dose of
- A) *2 mg.*
- B) *5 mg.*
- C) *10 mg.*
- D) *12 mg or greater.*

8. Duration of treatment with varenicline tartrate is
- A) *4 weeks.*
- B) *8 weeks.*
- C) *12 weeks.*
- D) *24 weeks.*

9. Which of the following statements regarding comorbid mental and substance use disorders is FALSE?
- A) *In the United States, 1 million adults have cooccurring mental and substance use disorders.*
- B) *No specific combinations of mental and substance use disorders are defined uniquely as co-occurring disorders.*
- C) *Patients with comorbid disorders demonstrate poorer treatment adherence and higher rates of treatment dropout than those without mental illness.*
- D) *Integrated treatment for comorbid drug use disorder and mental illness has been found to be consistently superior compared with separate treatment of each diagnosis.*

Test questions continue on next page ➞

10. Treatment of comorbid mental and substance use disorders should initially focus on
- A) *stabilization of the patient's substance use disorder.*
- B) *stabilization of the patient's mental health disorder.*
- C) *a goal of six to nine weeks abstinence before addressing comorbidities.*
- D) *any mental disorder symptoms that appear to resolve during abstinence.*

11. Which of the following ethical issue should be considered when caring for patients with substance use disorders?
- A) *Confidentiality*
- B) *Access to services*
- C) *Informed consent*
- D) *All of the above*

12. When opioids are used for acute pain, clinicians should prescribe
- A) *the highest safe dose.*
- B) *extended-release opioids.*
- C) *a quantity no greater than that needed for the expected duration of severe pain.*
- D) *All of the above*

13. A patient prescribed opioids for chronic pain who is 65 years of age and displays high levels of pain acceptance and active coping strategies is considered at what level of risk for developing problematic opioid behavioral responses?
- A) *Low*
- B) *Medium*
- C) *High*
- D) *Severe*

14. Certain questions are useful in screening to determine presence of substance use disorder. One such set of questions is known as the CAGE questionnaire. The CAGE acronym stands for
- A) *Confusion, Agitation, S3 Gallop, Edema.*
- B) *Cut down, Annoyed, Guilty, Eye-opener.*
- C) *Chloral hydrate, Alcohol, Glutethimide, Ethchlorvynol.*
- D) *un-Controllable urge to drink, un-Able to limit intake, un-Grateful for help to stop drinking, un-Excited about treatment.*

15. For patients considered at medium risk for misuse of prescription opioids, urine drug testing should be completed every
- A) *6 to 12 weeks.*
- B) *3 to 6 months.*
- C) *6 to 12 months.*
- D) *1 to 2 years.*

16. All of the following statements regarding the Concurrent Use of benzodiazepines in patients prescribed opioids is true, EXCEPT:
- A) *Opioids have the potential for drug dependence and addiction, but benzodiazepines do not.*
- B) *If a benzodiazepine is to be discontinued, the clinician should taper the medication gradually.*
- C) *In 2019, 16% of persons who died of an opioid overdose also tested positive for benzodiazepines.*
- D) *Combining benzodiazepines with opioids is unsafe because both classes of drug cause central nervous system depression and sedation and can decrease respiratory drive.*

17. Which of the following statements regarding the disposal of opioids is TRUE?
- A) *Patients are almost always advised of what to do with unused or expired medications.*
- B) *There are no universal recommendations for the proper disposal of unused opioids.*
- C) *According to the FDA, most medications should be flushed down the toilet instead of thrown in the trash.*
- D) *All of the above*

18. The most common source of nonmedical use of prescribed opioids is from
- A) *a friend or relative for free.*
- B) *a prescription from one doctor.*
- C) *purchase from a drug dealer or other stranger.*
- D) *theft from a doctor's office, clinic, hospital, or pharmacy.*

19. Which of the following behaviors is the most suggestive of an emerging opioid use disorder?
- A) *Asking for specific medications*
- B) *Injecting medications meant for oral use*
- C) *Reluctance to decrease opioid dosing once stable*
- D) *Stockpiling medications during times when pain is less severe*

20. Which government agency is responsible for formulating federal standards for the handling of controlled substances?
- A) *Institutes of Medicine*
- B) *U.S. Drug Enforcement Administration*
- C) *Office of National Drug Control Policy*
- D) *U.S. Department of Health and Human Services*

Be sure to transfer your answers to the Answer Sheet located on the envelope insert.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Pharmacologic and Medical Advances in Obesity Management

This course meets 4 hours of Patient Safety/Risk Management education.

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

Audience

This course is designed for all physicians, nurses, 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 has been designated for 15 Lifelong Learning (Part II) credits for the American Board of Pathology Continuing Certification Program.

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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

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.

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

BMI DEFINITIONS OF WEIGHT			
Weight Category	**BMI Definition (kg/m^2)**		
	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*

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

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].

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].

PREVALENCE OF OBESITY AND SEVERE OBESITY AMONG ADULTS AGED 20–74 YEARS						
Year	**Percent of Population Considered Obese (BMI ≥30 kg/m²)**			**Percent of Population Considered Severely Obese (BMI ≥40 kg/m²)**		
	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*

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].

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

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*

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*

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.

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].

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*

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

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].

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

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

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

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

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, American 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

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.)

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 fac-

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*

tors (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 medica-

tions 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)

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)

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 confidential 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].

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*

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].

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

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

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].

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.

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*

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].

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*

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].

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 RECOMMENDATIONS

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

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

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 cross-talk 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

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/Answer Sheet/Evaluation insert located between pages 60–61.

TEST QUESTIONS
#94280 PHARMACOLOGIC AND MEDICAL ADVANCES IN OBESITY MANAGEMENT

This is an open book test. Please record your responses on the Answer Sheet.
A passing grade of at least 80% must be achieved in order to receive credit for this course.

This 15 Credit activity must be completed by November 30, 2026.

1. A Black adult with a body mass index (BMI) of 28 would be considered
- A) *underweight.*
- B) *healthy weight.*
- C) *overweight.*
- D) *obese.*

2. In 2023, the AMA adopted a policy that recognizes the issues with BMI measurement and suggests that it be used in conjunction with other valid measures of risk. Which of the following is considered a valid measure of risk?
- A) *Visceral fat*
- B) *Body composition*
- C) *Genetic or metabolic factors*
- D) *All of the above*

3. During 2017–2018, which racial/ethnic group had the highest age-adjusted obesity prevalence in the United States?
- A) *Hispanic Americans*
- B) *Non-Hispanic Black Americans*
- C) *Non-Hispanic Asian Americans*
- D) *Non-Hispanic White Americans*

4. A 5-point increase in BMI is strongly associated with increased risk of all of the following, EXCEPT:
- A) *Thyroid and colon cancers in men*
- B) *Endometrial and gallbladder cancers in women*
- C) *Pancreatic and stomach cancers in East Asian individuals*
- D) *Esophageal adenocarcinoma and renal cancers in both sexes*

5. Basal energy expenditure is defined as
- A) *exercise and non-exercise activity.*
- B) *work-time (occupational) or leisure-time energy expenditure.*
- C) *the sum of basal energy expenditure and activity energy expenditure.*
- D) *the minimum energy required to maintain vital physiological functions.*

6. Increasing activity levels may bring diminishing returns due to
- A) *decreased activity intensity over time.*
- B) *compensatory responses in nonactivity energy expenditure.*
- C) *a predisposition to adiposity because they are weaker energy compensators.*
- D) *All of the above*

7. Which of the following statements regarding energy balance is FALSE?
- A) *The small storage capacity of fat can only cover overnight energy needs during sleep.*
- B) *As a substrate for energy metabolism, fat is last in the hierarchy that determines fuel selection.*
- C) *Excess energy is stored as fat in adipose depots, carbohydrate (as glycogen) in liver, or protein in muscle.*
- D) *The energy density of adipose tissue is nearly 10-fold greater than liver (glycogen) or muscle (protein).*

8. The Obesity Medicine Association (OMA) has identified four pillars of obesity care. These pillars are
- A) *psychotherapy, pharmacotherapy, environmental interventions, and lifestyle changes.*
- B) *healthful nutrition, physical activity, behavior modification, and medical management.*
- C) *cognitive-behavioral therapy, dialectical behavioral therapy, exercise therapy, and insulin.*
- D) *antiobesity medications, surgical interventions, hormone therapy, and medical nutrition therapy.*

9. Which of the following antidepressants is considered to be weight-reducing?
- A) *Paroxetine*
- B) *Bupropion*
- C) *Mirtazapine*
- D) *Amitriptyline*

10. Which of the following is a preferred agent for the patient with bipolar disorder for whom weight loss or maintenance is a concern?
- A) *Quetiapine*
- B) *Olanzapine*
- C) *Ziprasidone*
- D) *Risperidone*

11. A patient who achieves 7% reduction in body weight should expect to see
- A) *type 2 diabetes remission.*
- B) *remission in obstructive sleep apnea.*
- C) *improved physical and biomechanical function.*
- D) *nonalcoholic steatohepatitis (NASH) improvement.*

12. All antiobesity medications are considered pregnancy risk factor category
- A) *A.*
- B) *B.*
- C) *C.*
- D) *X.*

13. Which of the following is a common adverse effect of phentermine HCl?
- A) *Diarrhea*
- B) *Dry mouth*
- C) *Hyperactivity*
- D) *Abdominal pain*

14. Gelesis100 acts
- A) *by binding to melanocortin-4 receptor (MC4R) in the hypothalamus, downstream of the leptin signaling pathway.*
- B) *as a transient, space-occupying device in a swallowed capsule that absorbs water to expand and fill up the stomach to induce satiety.*
- C) *as a centrally acting sympathomimetic, with therapeutic effects mediated through increased levels of norepinephrine in the hypothalamus.*
- D) *as a pancreatic and gastric lipase inhibitor that blocks the lipase-catalysed breakdown and absorption of around 30% of dietary fats.*

15. Each naltrexone/bupropion tablet contains
- A) *8 mg naltrexone and 90 mg bupropion.*
- B) *18 mg naltrexone and 9 mg bupropion.*
- C) *80 mg naltrexone and 190 mg bupropion.*
- D) *90 mg naltrexone and 8 mg bupropion.*

16. Which of the following agents is a glucagon-like peptide-1 receptor agonist (GLP-1 RA)?
- A) *Orlistat*
- B) *Topiramate*
- C) *Semaglutide*
- D) *Diethylpropion*

17. Given the decreased likelihood of obesity in current cannabis users, which medication is being studied for possible antiobesity uses?
- A) *THC*
- B) *CBD*
- C) *Nabilone*
- D) *Dronabinol*

18. What is the recommended first-line antiobesity medication for obesity management?
- A) *Liraglutide 1.8 mg daily*
- B) *Semaglutide 2.4 mg weekly*
- C) *Orlistat 60 mg three times daily*
- D) *Phentermine/topiramate 7.5 mg/46 mg daily*

19. After initiating any antiobesity medication, the weight loss by what point is considered an indicator of treatment response?
- A) *2 weeks*
- B) *8 weeks*
- C) *12 weeks*
- D) *24 weeks*

20. Which of the following antiobesity medications is the least expensive?
- A) *Orlistat*
- B) *Liraglutide*
- C) *Phentermine*
- D) *Phentermine-topiramate ER*

21. Which of the following metabolic and bariatric surgery (MBS) options is optimally suited for a patient with lower BMI and no metabolic disease?
- A) *Sleeve gastrectomy*
- B) *Roux-en-Y gastric bypass (RYGB)*
- C) *Laparoscopic adjustable gastric banding (LAGB)*
- D) *Biliopancreatic diversion with duodenal switch (BPD/DS)*

Test questions continue on next page ➞

22. Which of the following statements regarding indications for MBS is TRUE?

A) Patients older than 70 years of age should not be offered MBS.

B) MBS is recommended for patients with BMI of 40 only in those with at least one obesity-related complication.

C) A BMI >25 suggests clinical obesity in Asian patients, and those with BMI >27.5 should be offered MBS.

D) MBS should be considered in patients with BMI 25–30 who do not achieve substantial or durable weight loss.

23. What should MBS candidates and patients be counseled regarding tobacco use?

A) Tobacco use, and cigarette smoking in particular, must be avoided at all times by all patients.

B) Patients who smoke cigarettes should stop as early as possible, preferably one year but at the very least six weeks before MBS.

C) Tobacco use should be avoided post-MBS given the increased risk of poor wound healing, anastomotic ulcer, and overall impaired health.

D) All of the above

24. All of the following intragastric balloon devices are ASMBS-endorsed and FDA-approved for six-month dwelltime, EXCEPT:

A) Orbera

B) Obalon

C) ReShape Duo

D) TransPyloric Shuttle

25. Brown adipose tissue

A) comprises 15% to 25% of body fat.

B) has more mitochondria (thus its brown appearance).

C) includes subcutaneous adipose tissue and visceral (abdominal) adipose tissue.

D) is absent in neonates but increases in adults and increases further in obese adults.

Be sure to transfer your answers to the Answer Sheet located on the envelope insert.

PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Full Course Availability List

✓	Course #	Course Title/Credits	Price

ALTERNATIVE MEDICINE

☐	98010	Cannabinoid Overview/3	$29
☐	98020	Commonly Abused Supplements/2	$23
☐	98030	Getting to the Point: Acupuncture and Acupoint Therapies/4	$36
☐	98060	Microbiome Medley: Pre-, Pro-, and Postbiotics/2.5	$23
☐	98070	The Scoop on Collagen/1.5	$23
☐	98080	Top-Selling Herbal Supplements/3	$29
☐	98090	Understanding Glucosamine and Chondroitin/1.5	$23
☐	98100	Complementary Therapies for Menopause/4	$36
☐	98320	Natural Psychedelics/3	$29
☐	98394	Herbal Medications: An Evidence-Based Review/10	$78

COMMUNITY HEALTH

☐	91413	Prescription Opioids: Risk Mgmt & Strategies for Safe Use/15	$113
☐	91514	Medical and Illicit Use of Anabolic Steroids/5	$43
☐	91534	A Review of Infertility/10	$78
☐	91544	Metabolic Syndrome: A Growing Epidemic/5	$43
☐	91573	Diagnosing and Treating Overweight and Obese Patients/5	$43
☐	91603	Prescribing Opioids: The West Virginia Requirement/3	$29
☐	91693	Families of Patients with Chronic Illness/10	$78
☐	91724	What Healthcare Professionals Should Know About Exercise/5	$43
☐	91743	Child, Adolescent, and Adult Immunization Schedules/5	$43
☐	91752	Chemical and Radiologic Injuries in Terrorist Attacks/1	$23
☐	91764	Bioterrorism: An Update for Healthcare Professionals/5	$43
☐	91784	Smoking and Secondhand Smoke/10	$78
☐	91793	Promoting the Health of Gender and Sexual Minorities/5	$43
☐	91803	Cancer Screening Among Racial/Ethnic Minority Women/5	$43
☐	91922	Clinical Care of the Transgender Patient/10	$78
☐	91943	Providing Culturally Responsive Care for Asian Immigrants/10	$78
☐	91953	Carpal Tunnel Syndrome/3	$29
☐	91983	The Role of Spirituality in Health and Mental Health/5	$43
☐	91993	Cancer Screening/10	$78

ETHICS - HUMAN RIGHTS

☐	47174	Medical Ethics for Physicians/5	$43
☐	97000	Implicit Bias in Health Care/3	$29
☐	97023	Sexual Assault/3	$29
☐	97032	The Intersection of Pain and Culture/5	$43
☐	97081	Sexual Harassment Prevention: The Illinois Requirement/1	$23
☐	97111	Recognizing and Reporting Human Trafficking in Florida/2	$23
☐	97143	Assessment and Management of Pain at the End of Life/2	$23
☐	97281	Pain Management Pearls: Opioids and Culture/2	$23
☐	97363	Cultural Meanings of Death and Dying/5	$43
☐	97383	Palliative Care and Pain Management at the End of Life/15	$113
☐	97430	Cultural Competence: An Overview/2	$23
☐	97440	Implicit Bias: The Michigan Requirement/2	$30
☐	97454	Violence in the Healthcare Workplace/5	$43
☐	97470	Human Trafficking and Exploitation: The Texas Requirement/5	$43
☐	97493	Digital Technology and Domestic Violence/3	$29
☐	97500	Imminent Death and Loss/1	$23
☐	97534	Child Abuse Identification & Reporting: The NY Requirement/2	$23
☐	97583	Child Abuse in Ethnic Minority and Immigrant Communities/10	$78
☐	97663	Online Professionalism and Ethics/3	$29
☐	97770	Counseling Patients at the End of Life/5	$43
☐	97791	Domestic and Sexual Violence/5	$43
☐	97824	Elder Abuse: Cultural Contexts and Implications/5	$43
☐	97914	Domestic Violence: The Kentucky Requirement/3	$29
☐	97923	Domestic Violence: The Florida Requirement/2	$23

GERIATRICS

☐	99083	Anemia in the Elderly/5	$43
☐	99143	Osteoporosis: Diagnosis and Management/5	$43

✓	Course #	Course Title/Credits	Price

INFECTION CONTROL / INTERNAL MEDICINE

☐	48763	Diagnosis & Mgmt of Chronic Kidney Disease in Primary Care/5	$43
☐	48853	Pressure Ulcers: Prevention and Management/10	$78
☐	94040	Monkeypox: The 2022 Global Outbreak/3	$29
☐	94082	Ebola Virus Disease/4	$36
☐	94093	The Mechanism-Based Approach to Pain Management/1	$23
☐	94102	Low Back Pain/15	$113
☐	94111	Pit Viper Snakebite Assessment and Treatment/10	$78
☐	94131	Neck Pain in Adults/10	$78
☐	94151	The Coronavirus Disease (COVID-19) Pandemic/2	$23
☐	94182	Viral Sexually Transmitted Infections/5	$43
☐	94214	Multidrug-Resistant Microbial Infections/5	$43
☐	94223	Hypertension: Strategies to Improve Outcomes/5	$43
☐	94301	Fibromyalgia/3	$29
☐	94343	Sepsis: Diagnosis and Management/4	$36
☐	94364	Malaria and the International Traveler/3	$29
☐	94424	Influenza: A Comprehensive Review/10	$78
☐	94454	Autoimmune Diseases/15	$113
☐	94523	Type 2 Diabetes: Treatment Strategies for Optimal Care/5	$43
☐	94554	Tuberculosis: An Update/5	$43
☐	94614	*Clostridioides difficile* Infection/5	$43
☐	94673	Pneumonia/10	$78
☐	94723	HIV/AIDS: Epidemic Update for Florida/1	$23
☐	94733	HIV/AIDS: Epidemic Update for Washington/7	$57
☐	94901	Gastroesophageal Reflux Disease in Adults/10	$78
☐	94924	Animal-Related Health Risks/15	$113
☐	94934	Rheumatoid Arthritis/5	$43
☐	94954	Osteoarthritis/10	$78
☐	94993	Viral Hepatitis/5	$43
☐	98401	Dizziness and Vertigo/10	$78
☐	98533	Smallpox Vaccination: An Update/5	$43
☐	98593	Multiple Sclerosis: A Comprehensive Review/10	$78
☐	98623	Foodborne Disease/10	$78
☐	98643	Infection Control: The New York Requirement/5	$43
☐	98663	Oral Pathology Review/5	$43
☐	98703	Chronic Pain Syn.: Current Concepts & Treatment Strategies/15	$113
☐	98712	Zika Virus Disease/3	$29
☐	98721	Bacterial Sexually Transmitted Infections/5	$43
☐	98772	Parkinson Disease/10	$78
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☐	98793	Food Allergies/5	$43
☐	98813	Chronic Obstructive Pulmonary Disease (COPD)/10	$78
☐	98883	Sleep Disorders/10	$78
☐	98903	HIV/AIDS: Epidemic Update/5	$43
☐	98932	Irritable Bowel Syndrome/10	$78

MANAGEMENT

☐	41032	Burnout in Physicians/5	$43
☐	41170	Professional Boundaries and Sexual Misconduct in Medicine/3	$29
☐	41234	OSHA and Healthcare Facilities/5	$43
☐	41473	Risk Management/5	$43
☐	91012	Family & Medical Leave: Law, Health Care, & Social Services/5	$43
☐	91042	Developing a Safe Opioid Treatment Plan for Managing Chronic Pain/1	$23
☐	91053	Health 2.0: Implications for Care/3	$29
☐	91140	HIPAA Privacy and Security/5	$43
☐	91283	Using Interpreters in Health and Mental Health Settings/5	$43
☐	91334	Medical Error Prevention and Root Cause Analysis/2	$23
☐	91380	Safe Handling of Hazardous Medications/2.5	$23
☐	91404	Clinical Trials: Considerations for Women and Ethnic Minorities/5	$43

Full Course Availability List *(Cont'd)*

✓	Course #	Course Title/Credits	Price

MEDICAL / SURGICAL

☐	40943	Acute Coronary Syndrome/15	$113
☐	40953	Moderate Sedation/5	$43
☐	90072	Migraine: Diagnosis and Therapeutic Advances/5	$43
☐	90120	Pulmonary Embolism/2	$23
☐	90200	Botulinum Toxin and Dermal Fillers for Facial Aging/10	$78
☐	90214	Diagnosing and Managing Headaches/10	$78
☐	90240	Pancreatic Cancer/10	$78
☐	90284	Ischemic Stroke/10	$78
☐	90373	Clinical Management of Ventricular Arrhythmias/15	$113
☐	90424	Seizures and Epilepsy Syndromes/10	$78
☐	90444	A Review of Interventional Radiology/10	$78
☐	90471	Safe Clinical Use of Fluoroscopy/10	$78
☐	90563	Disorders and Injuries of the Eye and Eyelid/15	$113
☐	90683	Oral Cancer and Complications of Cancer Therapies/5	$43
☐	90744	Transport Methods for Critically Ill Patients/15	$113
☐	90773	Skin Cancers/5	$43
☐	90782	Colorectal Cancer/15	$113
☐	90804	Antibradycardia Pacemakers/15	$113
☐	90823	Clinical Management of Atrial Fibrillation/10	$78
☐	90844	Hyperlipidemias & Atherosclerotic Cardiovascular Disease/10	$78
☐	90983	Bariatric Surgery for Weight Loss/5	$43
☐	95001	Expanding the Options: The Drug-Approval Process in the U.S./5	$43

MEN'S HEALTH

☐	93764	Men's Health Issues/15	$113
☐	93772	Male Sexual Dysfunction/10	$78
☐	93884	Prostate Cancer/5	$43

PEDIATRICS

☐	92073	Care of the Pediatric Trauma Patient/15	$113
☐	92203	Autism Spectrum Disorder/5	$43
☐	92343	Childhood Leukemias and Lymphomas/15	$113
☐	92404	Pediatric Abusive Head Trauma/1.5	$23

PHARMACOLOGY

☐	45121	Strategies for Appropriate Opioid Prescribing: The Florida Req/5	$43
☐	95073	Antibiotics Review/5	$43
☐	95082	Antidepressant-Associated Sexual Dysfunction/1	$23
☐	95102	An Introduction to Pharmacogenetic Testing/1	$23
☐	95131	Prescription Opioids & Pain Mgmt: The Tennessee Guidelines/2	$23
☐	95142	Optimizing Opioid Safety and Efficacy/15	$113
☐	95151	Responsible and Effective Opioid Prescribing/3	$29
☐	95172	Medical Marijuana and Other Cannabinoids/5	$43
☐	95211	Responsible Prescribing of Controlled Substances: The LA Req/3	$29
☐	95300	Substance Use Disorders & Pain Mgmt: MATE Act Training/8	$54
☐	95500	Opioid Safety: Balancing Benefits and Risks/5	$43

✓	Course #	Course Title/Credits	Price

PSYCHIATRIC / MENTAL HEALTH

☐	96012	Post-Traumatic Stress Disorder/15	$113
☐	96102	Frontotemporal Degeneration/2	$23
☐	96154	Alzheimer's Disease/15	$113
☐	96182	Anxiety Disorders/15	$113
☐	96213	Attention Deficit Hyperactivity Disorder/5	$43
☐	96222	Borderline Personality Disorder/15	$113
☐	96313	Human Trafficking and Exploitation/5	$43
☐	96342	Mental Health Issues Common to Veterans & Their Families/2	$23
☐	96404	Depression and Suicide/15	$113
☐	96411	Behavioral Addictions/15	$113
☐	96423	Cyberbullying and Harassment/5	$43
☐	96431	Mass Shooters and Murderers: Motives and Paths/15	$113
☐	96442	Suicide Assessment and Prevention/6	$50
☐	96473	Obsessive-Compulsive Disorder/4	$36
☐	96563	Alcohol and Alcohol Use Disorders/10	$78
☐	96690	Anxiety Disorders in Older Adults/3	$29
☐	96790	Psychedelic Medicine and Interventional Psychiatry/10	$78
☐	96912	Novel Psychoactive Substances: Trends in Drug Abuse/5	$43
☐	96944	Cocaine Use Disorder/5	$43
☐	96954	Methamphetamine Use Disorder/5	$43
☐	96963	Opioid Use Disorder/10	$78
☐	96973	Cannabis and Cannabis Use Disorders/5	$43
☐	96983	Hallucinogens/4	$36
☐	96993	Club Drugs/3	$29

WOMEN'S HEALTH - MATERNAL / CHILD

☐	93032	Female Sexual Dysfunction/5	$43
☐	93113	Contraception/5	$43
☐	93253	Bleeding During Pregnancy/10	$78
☐	93504	Meanings of Menopause: Cultural Considerations/5	$43
☐	93603	Vaginal and Uterine Bleeding/5	$43

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Selected Course Availability List

These courses may be ordered by mail on the Customer Information form located between pages 60–61.
We encourage you to **GO GREEN**. Access your courses **online** to save paper and **receive a discount**!
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MODERATE SEDATION
#40953 • 5 Credits
Book By Mail – $43 • ONLINE – $35
Purpose: The purpose of the course is to provide physicians with the information necessary to perform moderate sedation safely and according to existing guidelines in order to facilitate better patient care.
Audience: This course is designed for physicians in a variety of settings, including private practice, emergency department, radiology department, cardiac catheterization lab, and ambulatory surgery centers. The course is also of benefit to private practice physicians in family medicine and virtually all specialty areas.
Additional Approvals: ABIM, ABS, ABA, ABP

PROFESSIONAL BOUNDARIES AND SEXUAL MISCONDUCT IN MEDICINE
#41170 • 3 Credits
Book By Mail – $29 • ONLINE – $21
Purpose: The purpose of this course is to provide physicians and physician assistants with the knowledge and skills necessary to ethically and appropriately avoid boundary violations.
Audience: This course is designed for all physicians and physician assistants in all practice settings.
Additional Approvals: ABIM, ABS, ABA, ABP, ABPath

DIAGNOSIS AND MANAGEMENT OF CHRONIC KIDNEY DISEASE IN PRIMARY CARE
#48763 • 5 Credits
Book By Mail – $43 • ONLINE – $35
Purpose: The purpose of this course is to provide physicians and physician assistants with the information necessary to develop treatment regimens associated with optimal adherence and provide adequate patient education, counseling, and support to patients with chronic kidney disease.
Audience: This course is designed for all primary care physicians and physician assistants involved in the care of patients with kidney disease.
Additional Approvals: ABIM, ABS, ABA, ABPath

PULMONARY EMBOLISM
NEW!
#90120 • 2 Credits
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.
Audience: This course is designed for physicians, PAs, and nurses involved in assessing, triaging, and managing patients with suspected pulmonary embolism.
Additional Approvals: ABIM, ABS, ABA, ABPath

ISCHEMIC STROKE
UPDATE
#90284 • 10 Credits
Book By Mail – $78 • ONLINE – $70
Purpose: The early identification and management of the risk factors for ischemic stroke can lead to substantial health benefits and reductions in cost. However, research has documented gaps between healthcare professionals' knowledge and practice with respect to prevention, demonstrating that adherence to evidence-based or guideline-endorsed recommendations pertaining to all interventions for primary and secondary prevention are underutilized or ineffective. The purpose of this course is to provide needed information about the roles of diagnosis and screening, timely evaluation of individuals with suspected stroke, immediate treatment of stroke, and the elements of effective rehabilitation programs so that healthcare professionals may implement the necessary interventions appropriately.
Audience: This course is designed for physicians, nurses, and physician assistants in the primary care setting. Neurologists and other healthcare practitioners will also benefit from this course.
Additional Approvals: ABIM, ABS, ABA

AGITATION, SEDATION, AND DELIRIUM IN ADULT ICU PATIENTS
NEW!
#90180 • 5 Credits
Book By Mail – $43 • ONLINE – $35
Purpose: The purpose of this course is to provide prescribers and other healthcare professionals with the knowledge and skills necessary to identify and act to avoid or address agitation, inappropriate sedation, and delirium in ICU patients.
Audience: This course is designed for physicians, physician assistants, and nurses involved in the care of patients in intensive care units.
Additional Approvals: ABIM, ABS, ABA

All Faculty and Division Planners have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Prices are subject to change. Visit www.NetCE.com for a list of current prices.

Selected Course Availability List *(Cont'd)*

DEVELOPING A SAFE OPIOID TREATMENT PLAN FOR MANAGING CHRONIC PAIN

#91042 • 1 Credit

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to provide the information necessary for clinicians to formulate an opioid treatment plan for chronic pain that takes into consideration the risks and benefits of these agents and minimizes the potential for abuse.

Audience: This course is designed for physicians, pharmacists, nurses, and physician assistants involved in the care of patients prescribed opioids to treat pain.

Additional Approvals: ABIM, ABS, ABA

METABOLIC SYNDROME: A GROWING EPIDEMIC

#91544 • 5 Credits

Book By Mail – $43 • ONLINE – $35

Purpose: As metabolic syndrome continues to become a more prevalent problem in the United States, healthcare professionals will encounter patients with this constellation of symptoms on a more frequent basis. The purpose of this course is to educate healthcare professionals about the epidemiology and treatment of metabolic syndrome so they may better care for their patients.

Audience: This course is designed for healthcare professionals working with adults or adolescent patients who exhibit risk factors for metabolic syndrome.

Additional Approvals: ABIM, ABS, ABA, ABP

CANCER SCREENING

#91993 • 10 Credits

Book By Mail – $78 • ONLINE – $70

Purpose: The purpose of this course is to concisely provide the evidence-based guidelines and recommendations for cancer screening in order to improve healthcare professionals' adherence and ultimately increase overall screening rates, leading to improvements in public health.

Audience: This course is designed for physicians, physician assistants, and nurses who may intervene to improve cancer screening rates.

Additional Approvals: ABIM, ABS, ABPath

MATERNAL HEALTH DISPARITIES

#93010 • 4 Credits

Book By Mail – $36 • ONLINE – $28

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.

Audience: This course is designed for all healthcare providers who may intervene to improve peripartum and postpartum health care and reduce health disparities.

Additional Approvals: ABIM, ABS, ABP

PROSTATE CANCER

#93884 • 5 Credits

Book By Mail – $43 • ONLINE – $35

Purpose: Although prostate cancer is the most common cancer diagnosed in men, it has a relatively good prognosis when diagnosed and treated early. The purpose of this course is to educate healthcare professionals about the epidemiology, screening, diagnosis, and treatment of prostate cancer to ensure that the disease is diagnosed early and treated properly.

Audience: This course is designed for all physicians, nurses, surgical professionals, and social work/counseling groups involved in the care of patients with prostate cancer.

Additional Approvals: ABIM, ABS, ABPath

HYPERTENSION: STRATEGIES TO IMPROVE OUTCOMES

#94223 • 5 Credits

Book By Mail – $43 • ONLINE – $35

Purpose: The purpose of this course is to provide healthcare professionals with the information necessary to develop treatment regimens associated with optimal adherence and provide adequate patient education, counseling, and support to patients with hypertension.

Audience: This course is designed for all physicians, physician assistants, nurses, and pharmacy professionals involved in the care of patients with hypertension.

Additional Approvals: ABIM, ABS

AUTOIMMUNE DISEASES

#94454 • 15 Credits

Book By Mail – $113 • ONLINE – $105

Purpose: The purpose of this course is to provide healthcare professionals with the information necessary to diagnose and treat the most common autoimmune disorders according to evidence-based or guideline-endorsed recommendations in order to improve patient quality of life.

Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the diagnosis, treatment, and care of patients with autoimmune diseases.

Additional Approvals: ABIM, ABS, ABP

AN INTRODUCTION TO PHARMACOGENETIC TESTING

#95103 • 1 Credit

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to educate healthcare professionals about pharmacogenetics and its application in drug selection and therapeutic interventions.

Audience: This course is designed for physicians, nurses, physician assistants, pharmacists, and pharmacy technicians who assess and make decisions regarding the appropriate pharmacotherapy for their patients.

Additional Approvals: ABIM, ABS, ABP

Prices are subject to change.
Visit www.NetCE.com for a list of current prices.

Selected Course Availability List *(Cont'd)*

ALZHEIMER DISEASE

#96154 • 15 Credits

Book By Mail – $113 • ONLINE – $105

Purpose: In order to increase and maintain a reasonable quality of life for patients with Alzheimer disease throughout the course of the disease, caregivers must have a thorough knowledge and understanding of the disease. The purpose of this course is to provide clinicians with the skills to care for patients with Alzheimer disease in any setting as part of the interdisciplinary team.

Audience: This course is designed for clinicians who come in contact with patients with Alzheimer disease in hospitals, long-term care facilities, home health care, and the office.

Additional Approvals: ABIM, ABS, ABPath

SUICIDE ASSESSMENT AND PREVENTION

#96442 • 6 Credits

By Mail – $50 • ONLINE – $42

Purpose: The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of depression and suicide on patient health as well as the skills necessary to identify and intervene for patients at risk for suicide.

Audience: This course is designed for healthcare professionals who may identify persons at risk for suicide and intervene to prevent or manage suicidality.

Additional Approvals: ABIM, ABS, ABP

ANXIETY DISORDERS IN OLDER ADULTS

#96690 • 3 Credits

Book By Mail – $29 • ONLINE – $21

Purpose: Older adults are the fastest growing demographic in the world, and anxiety disorders are the most common mental disorder in this age group. The purpose of this course is to provide clinicians with the knowledge and skills necessary in order to improve the assessment and treatment of anxiety disorders in older adults.

Audience: This course is designed for the benefit of a broad range of allied health professionals, including but not limited to physicians, nurses, medical assistants, and nursing home administrators.

Additional Approvals: ABIM, ABS

PSYCHEDELIC MEDICINE AND INTERVENTIONAL PSYCHIATRY

#96790 • 10 Credits

Book By Mail – $78 • ONLINE – $70

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

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

Additional Approvals: ABIM, ABS, ABP

CANNABIS AND CANNABIS USE DISORDERS

#96973 • 5 Credits

Book By Mail – $43 • ONLINE – $35

Purpose: The purpose of this course is to allow healthcare professionals to effectively identify, diagnose, treat, and provide appropriate referrals for patients with cannabis use disorders.

Audience: This course is designed for health and mental health professionals who are involved in the evaluation or treatment of persons who use cannabis, either illicitly or as an adjunct to medical treatment.

Additional Approvals: ABIM, ABS, ABP

SEXUAL ASSAULT

#97023 • 3 Credits

By Mail – $29 • ONLINE – $21

Purpose: The purpose of this course is to address knowledge gaps, enhance clinical examination and management skills, and improve treatment outcomes for victims of sexual assault.

Audience: This course is intended for physicians and other healthcare professionals who may be called upon to provide care to victims of sexual assault.

Additional Approvals: ABIM, ABS, ABP, ABPath

IMPLICIT BIAS: THE MICHIGAN REQUIREMENT

#97440 • 2 Credits

ONLINE ONLY – $30

Purpose: The purpose of this course is to provide healthcare professionals with an overview of the impact of implicit biases on clinical interactions and decision making.

Audience: This course is designed for the interprofessional healthcare team and professions working in all practice settings in Michigan.

Additional Approvals: ABIM, ABS, ABA, ABP, ABPath

Special Approvals: This course meets 2 of the 3 hours of implicit bias education required for physicians and 2 hours required for physician assistants.

COUNSELING PATIENTS AT THE END OF LIFE

#97770 • 5 Credits

Book By Mail – $43 • ONLINE – $35

Purpose: 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.

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

Additional Approvals: ABIM, ABS

Prices are subject to change.
Visit www.NetCE.com for a list of current prices.

Selected Course Availability List *(Cont'd)*

COMPLEMENTARY THERAPIES FOR MENOPAUSE

#98100 • 4 Credits

Book By Mail – $36 • ONLINE – $28

Purpose: The purpose of this course is to help healthcare professionals in all practice settings increase their understanding of nutrients, lifestyle changes, complementary modalities, and herbal products that are often used during menopause.

Audience: This course is designed for healthcare professionals whose patients are taking or are interested in using complementary therapies to manage symptoms of menopause.

Additional Approvals: ABIM, ABS

INFECTION CONTROL: THE NEW YORK REQUIREMENT

#98643 • 5 Credits

By Mail – $43 • ONLINE – $35

Purpose: The purpose of this course is to provide a review of current infection control practices and accepted standards, with an emphasis on the application of infection control standards and practices in outpatient and ambulatory settings.

Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals in New York required to complete education to enhance their knowledge of infection control.

Additional Approvals: ABIM, ABS, ABA, ABP, ABPath

Special Approvals: This course is approved by the New York State Department of Health to fulfill the requirement for 4 hours of Infection Control Training as mandated by Chapter 786 of the Laws of 1992. Provider #OT10781.

Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of a course constitutes permission to share the completion data with ACCME.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the learner to earn credit toward the CME and Self-Assessment requirements of the American Board of Surgery's Continuous Certification program. It is the CME activity provider's responsibility to submit learner completion information to ACCME for the purpose of granting ABS credit.

Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

Designated activities contribute to the patient safety CME requirement for Part II: Lifelong Learning and Self-Assessment of the American Board of Anesthesiology's (ABA) redesigned Maintenance of Certification in Anesthesiology Program® (MOCA®), known as MOCA 2.0®. Please consult the ABA website, www.theABA.org, for a list of all MOCA 2.0 requirements.

Participants will earn CC points equivalent to the amount of CME credits claimed for the activity in the American Board of Pathology area of Lifelong Learning (Part II).

Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

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Price AFTER January 31, 2025
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ENCLOSED SPECIAL OFFER: 30 CREDITS

Complete all four courses or any combination of these four courses for a maximum payment of $105 (or pay the individual course price).

✓	Course #	Course Title / Credits	Price
	97542	Child Abuse Identification and Reporting: The Pennsylvania Requirement / 3 Credits	$21
	97510	Intercultural Competence and Patient-Centered Care / 4 Credits	$28
	95300	Substance Use Disorders and Pain Management: MATE Act Training / 8 Credits	$56
	94280	Pharmacologic and Medical Advances in Obesity Management / 15 Credits	$105

Additional Courses Available by Mail (ACCESS ONLINE FOR A DISCOUNT!)

Payment must accompany this form. To order by phone, please have your credit card ready.

✓	Course #	Course Title / Credits	Price
☐	40953	Moderate Sedation / 5	$43
☐	41170	Prof. Boundaries & Sexual Misconduct in Medicine / 3	$29
☐	48763	Diagnosis & Mgmt of Chronic Kidney Disease / 5	$43
☐	90120	Pulmonary Embolism / 2	$23
☐	90284	Ischemic Stroke / 10	$78
☐	90180	Agitation, Sedation, & Delirium in Adult ICU Patients / 5	$43
☐	91042	Developing a Safe Opioid Treatment Plan / 1	$23
☐	91544	Metabolic Syndrome: A Growing Epidemic / 5	$43
☐	91993	Cancer Screening / 10	$78
☐	93010	Maternal Health Disparities / 4	$36
☐	93884	Prostate Cancer / 5	$43
☐	94223	Hypertension: Strategies to Improve Outcomes / 5	$43
☐	94454	Autoimmune Diseases / 15	$113
☐	95103	An Introduction to Pharmacogenetic Testing / 1	$23
☐	96154	Alzheimer Disease / 15	$113
☐	96442	Suicide Assessment and Prevention / 6	$50
☐	96690	Anxiety Disorders in Older Adults / 3	$29
☐	96790	Psychedelic Medicine & Interventional Psychiatry / 10	$78
☐	96973	Cannabis and Cannabis Use Disorders / 5	$43
☐	97023	Sexual Assault / 3	$29
☐	97440	Implicit Bias: The MI Requirement (Online Only) / 2	Online Only
☐	97770	Counseling Patients at the End of Life / 5	$43
☐	98100	Complementary Therapies for Menopause / 4	$36
☐	98643	Infection Control: The New York Requirement / 5	$43

☐ Check or Money Order (*payable to NetCE*)
☐ VISA / MasterCard / AmEx / Discover

Please print name (as shown on credit card)

Credit card #

Expiration date / Security code

Security code is last three numbers in the signature area on back of credit card or four numbers above the account number on front of AmEx cards.

Signature

Special Offer (**BEFORE January 31, 2025**) **$105**

$150 (**AFTER January 31, 2025**)

I would like my certificates mailed for an additional $6

Additional Courses

Subtotal

Expedited Delivery

Grand Total

Expedited mail delivery within 2 to 3 days is available in most areas at an additional charge of $35. Call for information on international delivery.

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Answer Sheet

(Completion of this form is mandatory)

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Please note the following:

- In accordance with the *AMA PRA Category 1 Credit™* system, physicians must complete and pass a post-test to receive credit.
- A passing grade of at least 70% must be achieved on each course test in order to receive credit.
- Darken only one circle per question.
- Use pen or pencil; please refrain from using markers.
- **Information on the Customer Information form must be completed.**
- **Include the completed and signed mandatory Evaluation.** Your postmark or facsimile date will be used as your completion date.

#97542 CHILD ABUSE IDENTIFICATION AND REPORTING: THE PENNSYLVANIA REQUIREMENT—3 CREDITS

Please refer to pages 18–19.

Expiration Date: 07/31/25

May be taken individually for $21

	A	B	C	D		A	B	C	D
1.	❍	❍	❍	❍	6.	❍	❍	❍	❍
2.	❍	❍	❍	❍	7.	❍	❍	❍	❍
3.	❍	❍	❍	❍	8.	❍	❍	❍	❍
4.	❍	❍	❍	❍	9.	❍	❍	❍	❍
5.	❍	❍	❍	❍	10.	❍	❍	❍	❍

#97510 INTERCULTURAL COMPETENCE AND PATIENT-CENTERED CARE—4 CREDITS

Please refer to pages 39–40.

Expiration Date: 09/30/26

May be taken individually for $28

	A	B	C	D		A	B	C	D		A	B	C	D
1.	❍	❍	❍	❍	6.	❍	❍	❍	❍	11.	❍	❍	❍	❍
2.	❍	❍	❍	❍	7.	❍	❍	❍	❍	12.	❍	❍	❍	❍
3.	❍	❍	❍	❍	8.	❍	❍	❍	❍	13.	❍	❍	❍	❍
4.	❍	❍	❍	❍	9.	❍	❍	❍	❍	14.	❍	❍	❍	❍
5.	❍	❍	❍	❍	10.	❍	❍	❍	❍	15.	❍	❍	❍	❍

#95300 SUBSTANCE USE DISORDERS AND PAIN MANAGEMENT: MATE ACT TRAINING—8 CREDITS

Please refer to pages 65–66.

Expiration Date: 04/30/26

May be taken individually for $56

	A	B	C	D		A	B	C	D		A	B	C	D		A	B	C	D
1.	❍	❍	❍	❍	6.	❍	❍	❍	❍	11.	❍	❍	❍	❍	16.	❍	❍	❍	❍
2.	❍	❍	❍	❍	7.	❍	❍	❍	❍	12.	❍	❍	❍	❍	17.	❍	❍	❍	❍
3.	❍	❍	❍	❍	8.	❍	❍	❍	❍	13.	❍	❍	❍	❍	18.	❍	❍	❍	❍
4.	❍	❍	❍	❍	9.	❍	❍	❍	❍	14.	❍	❍	❍	❍	19.	❍	❍	❍	❍
5.	❍	❍	❍	❍	10.	❍	❍	❍	❍	15.	❍	❍	❍	❍	20.	❍	❍	❍	❍

#94280 PHARMACOLOGIC AND MEDICAL ADVANCES IN OBESITY MANAGEMENT—15 CREDITS

Please refer to pages 112–114.

Expiration Date: 11/30/26

May be taken individually for $105

	A	B	C	D		A	B	C	D		A	B	C	D
1.	❍	❍	❍	❍	11.	❍	❍	❍	❍	21.	❍	❍	❍	❍
2.	❍	❍	❍	❍	12.	❍	❍	❍	❍	22.	❍	❍	❍	❍
3.	❍	❍	❍	❍	13.	❍	❍	❍	❍	23.	❍	❍	❍	❍
4.	❍	❍	❍	❍	14.	❍	❍	❍	❍	24.	❍	❍	❍	❍
5.	❍	❍	❍	❍	15.	❍	❍	❍	❍	25.	❍	❍	❍	❍
6.	❍	❍	❍	❍	16.	❍	❍	❍	❍					
7.	❍	❍	❍	❍	17.	❍	❍	❍	❍					
8.	❍	❍	❍	❍	18.	❍	❍	❍	❍					
9.	❍	❍	❍	❍	19.	❍	❍	❍	❍					
10.	❍	❍	❍	❍	20.	❍	❍	❍	❍					

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Evaluation

(Completion of this form is mandatory)

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Please read the following questions and choose the most appropriate answer for each course completed.

1. Was the course content new or review?
2. How much time did you spend on this activity, including the questions?
   (Physicians should only claim credit commensurate with the extent of their participation in the activity.)
3. Would you recommend this course to your peers?
4. Did the course content support the stated course objective?
5. Did the course content demonstrate the author's knowledge of the subject?
6. Was the course content free of bias?
7. Before completing this course, did you identify the necessity for education on the topic to improve your professional practice?
8. Have you achieved all of the stated learning objectives of this course?
9. Has what you think or feel about this topic changed?
10. Did evidence-based practice recommendations assist in determining the validity or relevance of the information?
11. Are you more confident in your ability to provide patient care after completing this course?
12. Do you plan to make changes in your practice as a result of this course content?
13. May we contact you later regarding planned changes in your practice and changes in treatment or health status of your patients as a result of this activity?

In accordance with the reporting requirements of Act 31, please provide the following information for course #97542.

14. Please provide the last four digits of your social security number.
15. Please provide your date of birth.

#97542 3 Credits	#97510 4 Credits	#95300 8 Credits	#94280 15 Credits
1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review
2. _____ Hours	2. _____ Hours	2. _____ Hours	2. _____ Hours
3. ☐ Yes ☐ No	3. ☐ Yes ☐ No	3. ☐ Yes ☐ No	3. ☐ Yes ☐ No
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. ☐ Yes ☐ No	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
14. __ __ __ __			
15. __/__/____ (mm/dd/yyyy)			

#97542 Child Abuse Identification and Reporting: The Pennsylvania Requirement — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

#97510 Intercultural Competence and Patient-Centered Care — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

#95300 Substance Use Disorders and Pain Management: MATE Act Training — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

#94280 Pharmacologic and Medical Advances in Obesity Management — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

Signature _____

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Course #	Credits	Price	Course #	Credits	Price	Course #	Credits	Price
Sub Total $			**Sub Total $**			**Sub Total $**		
						Total Price $		

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