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Sexual Harassment Prevention: The Illinois Requirement

If you are NOT licensed in Illinois, you may skip this course, or complete and receive one hour of general credit.

Audience
This course is designed for nurses, physicians, physician assistants, pharmacists, social workers, therapists, and all members of the interprofessional healthcare team who may act to prevent sexual harassment.

Course Objective
The purpose of this course is to provide health and mental health professionals with clear knowledge of the consequences of sexual harassment and the skills to help combat harassment in the workplace.

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

1. Describe the primary types and forms of sexual harassment.
2. Identify the consequences of sexual harassment.
3. Discuss steps to take when one witnesses or experiences sexual harassment.
4. Outline whistleblower protections.

Faculty
Lauren E. Evans, MSW, received her Master's degree in Social Work from California State University, Sacramento, in 2008. Her focus was on political and community social work. She has also been a Registered International Instructor of Therapeutic Horseback Riding through the Professional Association of Therapeutic Horsemanship International (PATH Intl.) since 2006. She currently works as a mental health practitioner with the homeless population.

Faculty Disclosure
Contributing faculty, Lauren E. Evans, MSW, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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

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Special Approvals

This course is designed to fulfill the Illinois requirement for 1 hour of continuing education in the area of sexual harassment prevention.

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

INTRODUCTION

Sexual harassment in the workplace has existed for centuries, primarily affecting domestic workers, servants, and women who were in the workforce. It was often assumed that women wanted or deserved the sexual attention and advances that they reported, unless they had substantial evidence that they had rejected or fought against their aggressor [1]. Only in recent decades has the law protected workers from the harassment and assault that many experienced.

Under Title VII of the Civil Rights Act of 1964, unwanted sexual advances in the workplace were made illegal, but it was not until the 1970s that the term "sexual harassment" began to gain recognition, due in large part to the women's rights movement [1; 2]. While sexual harassment is a term that has been familiar to the general population for the past 40 years, it has returned to the spotlight since the beginning of the "Me Too" movement, which started in 2006 but gained more widespread support and following in 2017 [3].

In 2021, the Equal Employment Opportunity Commission (EEOC) received approximately 21,270 reports of harassment from employees in the private sector and in local and state governments [4]. In 2015, the EEOC received 6,741 harassment reports from federal employees. In both cases, 45% of the reports were alleged cases of sexual harassment. According to the EEOC, approximately 90% of employees who experience harassment in the workplace never take formal action against their harasser [4; 5]. Overall, it is estimated that between 25% and 85% of women experience sexual harassment at work [5]. While women make up the large majority of sexual harassment victims, men are also victims. In 2018, men filed slightly less than 16% of all sexual harassment claims made to the EEOC [4].

The field of health care has several risk factors that make it particularly prone to incidents of sexual harassment. For example, sexual harassment occurs more often in workplaces with hierarchal structures and significant power disparities, both of which are apparent in healthcare workplaces. Also, harassment is more common in workplaces that are male-dominated [5; 6]. In one survey, 30% to 70% of female physicians and 50% of female medical students reported having experienced sexual or gender harassment at work [6; 7]. Sexual harassment has also been found to be particularly common in the field of nursing [8]. In one survey of nursing students, 60% reported having experienced sexual harassment [9]. In mental health care, a study of workers at an acute psychiatric facility found that 9.5% to 37.2% had experienced sexual harassment perpetrated by a patient/client [10]. It is important to note that the incidence of sexual harassment is difficult to determine, as most studies of workplace violence do not distinguish physical from verbal violence/threats or sexual harassment.

It was once thought that sexual harassment was something workers had to put up with it in order to advance in the healthcare field [8]. However, it is important that all employees know that sexual harassment is not something that should be endured, regardless of the setting. In 2017, TIME'S UP Healthcare was founded, with a mission of helping change culture, companies, and laws. The TIME'S UP Foundation aims to create a society free of gender-based discrimination in the workplace and beyond [7].

This course will discuss the laws and regulations that define sexual harassment and the many consequences victims may experience. Steps to take in order to report sexual harassment if one experiences or witnesses it in the workplace will also be outlined. Lastly, this course will review the laws in place to protect those who make a report.

DEFINING SEXUAL HARASSMENT

Sexual harassment is a form of sex discrimination, violating Title VII of the Civil Rights Act of 1964. According to the EEOC, [11]:

> ...unwelcome sexual advances, requests for sexual favors, and other verbal or physical conduct of a sexual nature constitutes sexual harassment when submission or rejection of this conduct explicitly or implicitly affects an individual's employment, unreasonably interferes with an individual's work performance, or creates an intimidating, hostile, or offensive work environment.

Psychologically, sexual harassment has been divided into three categories that reflect the legal definitions [12]:

- Gender harassment: Insults based upon sex, jokes, sexist comments, sexting, pornography, dehumanizing epithets (e.g., dog, whore), grabbing
- Unwanted sexual attention: Attraction, sexual pursuit, pressure for dates, unwanted compliments, the sharing of sexual fantasies—a show of sexual interest that is unwelcome
- Sexual coercion: Sexual compliance as a condition of a relationship

Among these three types, gender harassment is the most common.

Victims of sexual harassment can be either men or women, although, as discussed, women are more likely to be victims of sexual harassment than men [4]. The harasser can be of the same or different sex as the victim (e.g., a man may harass a woman or another man). Additionally, it is possible that a victim is not the target of the harasser but was affected by offensive behavior that was targeted toward another person. Harassers may be the victim's supervisor, employer, co-worker, or even a non-employee (e.g., client, patient) [11].

TYPES AND FORMS OF SEXUAL HARASSMENT

There are two categories of sexual harassment as outlined by Title VII of the Civil Rights Act of 1964: quid pro quo and hostile work environment [13; 14].

Quid Pro Quo

What is quid pro quo sexual harassment?

Quid pro quo, meaning "this for that" in Latin, consists of a supervisor or other superior asking for sexual favors in exchange for benefits at work. These demands may be outright or implied. Benefits may include a promotion, a pay increase, a bigger office, approval of vacation time, better work shifts, or keeping one's job. Quid pro quo harassment also includes negative repercussions from refusing to perform the acts requested by the superior. For example, the harasser may threaten to or actually fire, demote, or assign unpleasant work assignments or bad work shifts to the victim as retaliation.

According to the law, even if a person acquiesced to the advances of a superior at first, she or he can report the sexual harassment at a later time [15]. Also, it may be possible for a third-party to be affected by and report sexual harassment—for example, if he or she was denied a promotion because another person submitted to the advances of a superior.

Hostile Work Environment

Hostile work environment sexual harassment is similar to quid pro quo in that it may involve sexual advances. However, a key difference is that the harasser may not offer benefits or threats. Also, the harassment may not come from a supervisor but rather a coworker, vendor, client, or patient. It includes unwanted and unwelcome advances, comments, jokes, or any other content that is offensive, hostile, or threatening and that affects or even prevents the employee from doing her or his job. This may include but is not limited to [16]:

- The telling of sexual or "dirty" jokes or stories
- The use of offensive or derogatory sexual language to refer to someone
- Speaking offensively and sexually about a person's gender in general
- Showing the victim offensive sexual images
- Any physical contact of a sexual or unnecessarily intimate nature that is repeated and is done without the permission of the victim

In cases of hostile work environment sexual harassment, a third-party may be the unintended victim—for example, if he or she overhears offensive jokes or speech and it affects work performance.

LAWS AND REGULATIONS DEFINING SEXUAL HARASSMENT

Title VII of the Civil Rights Act of 1964

As noted, Title VII of the Civil Rights Act of 1964 is a federal law that protects workers from discrimination regardless of their gender, race, color, national origin, or religion [2]. The EEOC was created under Title VII and is responsible for enforcing federal laws that make it illegal to discriminate against a job applicant or an employee. This law applies to businesses with 15 or more employees and to federal, state, and local governments. Violation of Title VII can encompass all aspects of employment, including but not limited to hiring, firing, layoffs, compensation, training, promotions, and assignments. It is also illegal to discriminate against a person for making a complaint or reporting discrimination [17; 18; 19]. Specifically, section 703 of Title VII states it shall be an unlawful employment practice for an employer to [19]:

- Fail or refuse to hire or to discharge any individual, or otherwise to discriminate against any individual with respect to his/her compensation, terms, conditions, or privileges of employment, because of such individual's race, color, religion, sex, or national origin
- Limit, segregate, or classify his/her employees or applicants for employment in any way that would deprive or tend to deprive any individual of employment opportunities or otherwise adversely affect his/her status as an employee, because of such individual's race, color, religion, sex, or national origin

29 C.F.R. Part 1604.11

The Code of Federal Regulations Part 1604.11 states that sexual harassment directly defies section 703 of Title VII of the Civil Rights Act of 1964 [20]. The Code reads [20]:

> Unwelcome sexual advances, requests for sexual favors, and other verbal or physical conduct of a sexual nature constitute sexual harassment when (1) submission to such conduct is made either explicitly or implicitly a term or condition of an individual's employment, (2) submission to or rejection of such conduct by an individual is used as the basis for employment decisions affecting such individual, or (3) such conduct has the purpose or effect of unreasonably interfering with an individual's work performance or creating an intimidating, hostile, or offensive working environment.

Illinois Laws

There are several laws in the state of Illinois regarding the prevention of, training to prevent, and protection from sexual harassment. The Illinois Human Rights Act, enforced by the Illinois Department of Human Rights (IDHR), ensures the right of all employees to work in an environment free of sexual harassment or discrimination [21]. In 2017, the Illinois Sexual Harassment and Discrimination (SHD) helpline and website were created in order to help inform and guide employees through the sexual harassment reporting process (***Resources***). The state of Illinois also requires that places of business have sexual harassment policies in place in order to protect employees and ease the reporting process [21; 22; 23].

CONSEQUENCES OF SEXUAL HARASSMENT

What are the negative psychological consequences of workplace sexual harassment?

Sexual harassment and worker bullying in the healthcare workplace have led to severe patient care failures, including medication and medical errors and even death [24]. In addition to patient care failures, research clearly demonstrates that sexual harassment can negatively affect one's health. People who have been victims of sexual harassment are more likely to be depressed and to have symptoms of stress and anxiety, including post-traumatic stress disorder (PTSD). Sexual harassment has been associated with additional negative psychologic effects, including burnout, unhealthy eating behaviors, self-blame, reduced self-esteem, emotional exhaustion, anger, disgust, fear, and less satisfaction with life in general. Furthermore, victims of sexual harassment may be more likely to abuse drugs and alcohol and self-harm. Physical health consequences may include headaches, exhaustion, disrupted sleep, gastrointestinal problems, weight gain or loss, and cardiovascular and respiratory issues [5; 13].

Sexual harassment has been shown to lower productivity in the workplace. This is partly due to the fact that victims of sexual harassment may spend work hours filing complaints, discussing the harassment with coworkers, or seeking assistance to stop the harassment. Victims may be tardy, may neglect their duties or assignments, or may be absent from work altogether. Sexual harassment in the workplace can negatively affect the entire team, creating a tense, uncomfortable environment for all employees.

Employee turnover is higher when there is harassment in the workplace [5; 13]. Women who are sexually harassed in the workplace are 6.5 times more likely to quit than women who are not. This results in women missing out on promotions and salary increases, thus increasing the wage gap between men and women [25].

In 1994, a study found that sexual harassment was conservatively estimated to have cost the U.S. government $327.1 million over two years [5; 25]. Factoring in inflation, this would amount to more than $556 million today [25]. This estimate included the costs of lowered productivity, sick leave, and job turnover, and did not include the cost incurred due to the damaged reputation of a company, which may affect its ability to attract employees or clients in the future [5].

WHAT TO DO IF ONE EXPERIENCES OR WITNESSES UNWELCOME SEXUAL CONTACT

What steps should a victim of sexual harassment take?

It is important to note that prevention of sexual harassment and the creation of a safe work environment is the responsibility of the employer. Clear policies should be put in place stating that sexual harassment of any kind will not be tolerated and that harassers will be disciplined or terminated. Unfortunately, national studies indicate that more than 70% of U.S. workplaces do not have institutional policies to address workplace violence, including sexual harassment [26]. Employees should have clear instructions for reporting, if need be, and retaliation against employees who file a report should not be tolerated [5; 21; 27].

If one experiences or witnesses sexual harassment in one's place of work, there are several things that can be done to stop the behavior and/or protect oneself [11; 13; 21]:

- It is important that the victim of sexual harassment not blame her- or himself. The blame should be put on the harasser.
- The victim should report the offending behavior to a superior or otherwise follow the grievance system that the employer has in place.
- If possible, document all incidents of sexual harassment, including when it occurred, what happened, what was said or implied, and who was present.
- The victim should make clear to the harasser that his or her behavior, speech, or actions are unwelcome and must stop. This may feel uncomfortable to the victim, but it is often the most effective strategy. If a face-to-face discussion is too difficult or dangerous, the victim may choose to send an e-mail or memo to the harasser outlining the incidents and explaining her or his feelings.
- If one feels comfortable, one may confide in a friend, family member, or coworker. This may help to reduce stress and receive support. Additionally, one may learn that he or she has not been the only one to experience sexual harassment from a particular harasser and a plan to report may be made.

- Seeking counseling may help reduce stress related to the sexual harassment.
- If the victim belongs to a union, it may be effective to report the harassment directly to the labor union.

If the employer has not effectively stopped the harassment, has not taken the complaint seriously, the sexual harassment has continued, or the victim has experienced retaliation after filing their complaint, the victim may then choose to report the harassment to the Illinois Department of Human Rights or file a civil lawsuit under Title VII of the Civil Rights Act of 1964.

REPORTING SEXUAL HARASSMENT

IN THE WORKPLACE

The first step to reporting sexual harassment in one's place of work is to report the harassment to a supervisor, human resources director, or manager. There should be a policy in place to support the victim and guide them through the reporting process. The policy should include the definition of sexual harassment, descriptions and examples of sexual harassment, and the penalties of violating the sexual harassment policy [15]. In most cases, the employer will conduct an investigation and take action, if indicated.

TO OUTSIDE ENTITIES

Illinois Department of Human Rights

A charge of discrimination, including sexual harassment, can be reported to the IDHR in person or by phone, fax, e-mail, or mail within 300 days of the alleged harassment. The employee who wishes to report sexual harassment must complete, sign, and submit a complainant information sheet (CIS) to the IDHR. More information, including the CIS and the locations and addresses to which one can make the report, can be found online at https://www.illinois.gov/dhr [15]. If the harassment occurs in the context of an educational institution, the IDHR has a specific form for reporting. In all other places of employment, the general employment CIS should be used to report sexual harassment.

After a report is made to the IDHR, an investigation begins. The IDHR may collect relevant documentation and/or speak to witnesses. The IDHR has up to 365 days to complete their investigation, but most cases are closed sooner. If the IDHR finds that there is substantial evidence of harassment, the case is taken to an administrative law judge at the Illinois Human Rights Commission, a separate state agency that conducts public hearings. This process can take several years [23].

The IDHR may also assist with mediation services in order to resolve any allegations and to avoid an investigation. An investigation can also be avoided if the two parties agree to a voluntary settlement [23].

Equal Employment Opportunity Commission

Another option for employees who experience sexual harassment is to file a complaint with the EEOC, the federal agency that enforces Title VII of the Human Rights Act of 1964. The EEOC will investigate allegations of harassment and determine if it is severe or pervasive enough to be considered illegal [18].

WHISTLEBLOWER PROTECTIONS

FEDERAL PROTECTIONS

What actions are considered retaliation if done in response to an employee's action with the EEOC?

Under equal employment opportunity (EEO) law, it is illegal to retaliate against a person for [28]:

- Filing or being a witness in an EEO charge, complaint, investigation, or lawsuit
- Communicating with a supervisor or manager about employment discrimination, including harassment
- Answering questions during an employer investigation of alleged harassment
- Refusing to follow orders that would result in discrimination
- Resisting sexual advances or intervening to protect others

An action is considered retaliation if, in response to an employee's action with the EEOC, the employer or supervisor [28]:

- Reprimanded the employee or gave a performance evaluation that was lower than it should have been
- Transferred the employee to a less desirable position
- Engaged in verbal or physical abuse
- Threatened to make, or actually made, reports to authorities (such as reporting immigration status or contacting the police)
- Engaged in increased scrutiny
- Spread false rumors
- Treated a family member negatively (e.g., canceled a contract with the person's spouse)
- Made the person's work more difficult (e.g., purposefully changing an employee's work schedule to conflict with family responsibilities)

ILLINOIS PROTECTIONS

The Illinois Human Rights Act explicitly protects employees from retaliation from their employer or supervisor in cases of discrimination and harassment. Retaliation is defined as conduct intended to punish, deter, or dissuade a person from making a complaint or filing a report of sexual harassment or discrimination, or participating in an investigation conducted by the Illinois Department of Human Rights or other similar agency [29; 30].

CONCLUSION

Sexual harassment in the workplace can be prevented and/or discouraged with training, anti-harassment policies, and reporting. Employers are responsible for creating work environments that are safe for all employees and are free from harassment. Following the correct state and federal reporting guidelines and having a clear understanding of what constitutes sexual harassment can help to reduce cases of harassment and provide a safe environment for all.

RESOURCES

Illinois Sexual Harassment and Discrimination Helpline
(877) 236-7703
https://www2.illinois.gov/sites/sexualharassment

Illinois Department of Human Rights
Chicago Office: (312) 814-6200
Springfield Office: (217) 785-5100
https://www2.illinois.gov/dhr

Illinois Legal Aid Online
https://www.illinoislegalaid.org

TIME'S UP Healthcare
https://timesupfoundation.org

U.S. Equal Employment Opportunity Commission
https://www.eeoc.gov

Customer Information/Evaluation insert located between pages 40–41.

Frontotemporal Dementia

Audience
This course is designed for nurses, physicians, and allied health and mental health professionals who may intervene to support patients with frontotemporal dementia and their families.

Course Objective
The purpose of this course is to provide healthcare professionals with current information on frontotemporal dementia (FTD). Understanding the epidemiology, pathology, clinical features, diagnostic process, genetics, symptom treatment/management, role of brain autopsy, and current research provides a foundation for the care of patients with FTD and support for their families.

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

1. Describe the epidemiology of frontotemporal dementia (FTD) in the United States.
2. Explain the brain changes of FTD and their general clinical manifestations.
3. Identify the three general presentations of FTD.
4. Review how a clinical diagnosis of FTD is made, including differentiation from Alzheimer disease.
5. Summarize the role of genetics in FTD.
6. Discuss strategies for managing symptoms of FTD and providing support to family caregivers.
7. Identify goals of current research on FTD.

Faculty
Ellen Steinbart, RN, MA, received a Bachelor of Arts from Macalester College in 1972, a Bachelor of Science in Nursing from Cornell University-New York Hospital School of Nursing in 1974, and a Master of Arts from the University of Washington School of Nursing in 1979. She worked as a hospital medical-surgical nurse and an intensive-care burn unit nurse, and she taught medical-surgical nursing at the University of Washington School of Nursing. For 25 years, she was a research nurse at the University of Washington, coordinating research projects on the role of genetics in dementia, including frontotemporal degeneration. She is now retired.

Lauren E. Evans, MSW, received her Master's degree in Social Work from California State University, Sacramento, in 2008. Her focus was on political and community social work. She has also been a Registered International Instructor of Therapeutic Horseback Riding through the Professional Association of Therapeutic Horsemanship International (PATH Intl.) since 2006. She currently works as a mental health practitioner with the homeless population.

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

Contributing faculty, Lauren E. Evans, MSW, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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EVIDENCE-BASED PRACTICE RECOMMENDATION

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

INTRODUCTION

Frontotemporal dementia (FTD) is a group of degenerative brain disorders characterized by behavior and language problems and also overlapping with some motor/movement diseases. FTD causes progressive deterioration in a person's ability to function as the result of damage to the frontal and temporal lobes of the brain. FTD is also referred to as frontotemporal degeneration, frontotemporal lobar degeneration, and Pick disease.

Dr. Arnold Pick, a Czech neurologist, psychiatrist, and neuropathologist, first described frontal and temporal lobe atrophy causing dementia and progressive aphasia in 1892 [1]. The clinical syndrome subsequently became known as "Pick disease." FTD is the third leading cause of dementia across all age groups, after Alzheimer disease (AD) and Lewy body dementia [2]. It is one of the most common causes of early-onset dementia, with onset typically between 45 and 64 years of age [2; 3].

The clinical presentation of FTD can be complex, and obtaining an accurate diagnosis can be challenging. The unique clinical symptoms of FTD, neuropsychologic assessment, and brain imaging can help distinguish it from AD and other dementias. There is presently no effective treatment for FTD, and symptom management can be challenging for healthcare providers and family caregivers. Research is in progress to better understand FTD, hopefully leading to effective treatment, cure, and prevention of this devastating disease.

EPIDEMIOLOGY OF FTD

It is estimated that FTD affects approximately 60,000 people in the United States [3]. As noted, the age of onset for FTD is typically 45 to 64 years, with a mean of 58.5 years and a reported range between 21 and 80 years of age [2; 3; 4; 5]. In the United States, the prevalence in people 45 to 64 years of age is estimated at 15 to 22 per 100,000 population; the incidence in this group is 2.7 to 4.1 per 100,000 [5]. It is estimated that 60% of those with FTD have onset between 45 and 64 years of age; 10% have onset before 45 years of age, and 30% have onset after 64 years of age [5]. FTD is now considered by some to be the most common form of pre-senile dementia in patients younger than age 60, even more common than AD in this group [6; 7; 8].

FTD affects both men and women. However, it is unclear if men and women are affected equally, or if some subtypes of FTD may be more common in one gender or the other [9]. Significant time (average: 3.6 years) often passes between symptom onset and actual clinical diagnosis [5].

The disease duration for FTD can range from 2 to 20 years from symptom onset to death, with a mean duration of 6 to 13 years [3; 5]. Pneumonia is the most common cause of death [3].

PATHOGENESIS AND PATHOPHYSIOLOGY OF FTD

Which areas of the brain are typically atrophied in patients with FTD?

Patients with FTD experience a progressive loss of neurons in the frontal and anterior temporal lobes, resulting in atrophy in these areas of the brain. They may also develop gliosis in the frontal and temporal lobes where neurons have been lost or damaged.

In FTD, affected neurons have an abnormal accumulation of protein within the cell, called inclusions. Three types of intra-neuronal inclusions have been identified, based on the protein involved. In some cases, the inclusions are composed of an abnormal form of the protein tau. In other patients, the inclusions are composed of the transactive response DNA-binding protein 43 (TDP-43). In a smaller number of FTD cases, the inclusions are composed of fused in sarcoma (FUS) protein [10].

The frontal and anterior temporal lobes of the brain control executive functions (e.g., planning, organizing, abstract thinking, judgment, decision making), personality, social behavior, and language. The changes associated with FTD causes impairments in executive function, personality, behavior, and/or language. The location of the neurodegeneration correlates fairly well with the clinical presentation [10]. Changes in other areas of the brain may cause overlapping movement problems. While the cause of most cases of FTD is not known, some cases are now known to be caused by genetic mutations.

CLINICAL PRESENTATION

FTD causes a gradual, progressive decline in behavior and/or language; movement disorders may also be involved. Behavior or language problems are typically the first and most prominent symptoms of FTD, whereas memory problems are the first symptoms of AD [5]. Subtypes of FTD have been identified based on clinical presentation (***Table 1***). Behavioral variant FTD (bvFTD) is the most common form and involves changes in behavior, personality, and emotions. Language presentations are referred to as primary progressive aphasia (PPA) and can take one of three forms: nonfluent/agrammatic variant PPA (nfvPPA), semantic variant PPA (svPPA), or logopenic variant PPA (lvPPA) [11]. Nonfluent/agrammatic PPA begins with problems in speech production, while svPPA involves impaired word comprehension and object recognition and lvPPA involves word-finding problems. A

FORMS OF FRONTOTEMPORAL DEGENERATION
Behavioral presentation • Behavioral variant FTD (bvFTD)
Language presentation, variants of primary progressive aphasia (PPA) • Nonfluent/agrammatic PPA (nfvPPA), previously called progressive non-fluent aphasia (PNFA) • Semantic variant PPA (svPPA), previously called semantic dementia (SD) • Logopenic variant PPA (lvPPA) (often found to have Alzheimer disease pathology at autopsy)
Associated movement disorders (not classified as FTD, but have shared symptoms) • Corticobasal syndrome (CBS) • Progressive supranuclear palsy (PSP) • Motor neuron disease, also called amyotrophic lateral sclerosis (FTD/MND or FTD/ALS)
Source: Compiled by Author *Table 1*

BEHAVIORAL VARIANT FTD	
Major Clinical Features	**Examples**
Disinhibition	Making inappropriate comments, taking food off someone else's table at a restaurant, telling sexual jokes, shoplifting, hitting
Apathy	Less involved in old hobbies or activities, deterioration in personal hygiene
Loss of empathy	Indifferent when a family member is hurt
Compulsive behaviors	Repeating the same phrase, clapping hands in the same pattern repeatedly, checking the time repeatedly
Hyper-oral behaviors	Overeating, eating one certain type of food, eating excessive sweets
Impaired executive function	Poor performance at work, poor financial decisions, difficulty planning and preparing a meal
Source: Compiled by Author	*Table 2*

movement presentation may appear as progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), or motor neuron disease (MND). Some patients may present with symptoms that overlap the different subtypes of FTD or may develop symptoms of other subtypes of FTD as the disease evolves. As more is learned about FTD, the terminology and classification of the subtypes may be revised.

BEHAVIORAL PRESENTATION

Behavioral Variant FTD

As noted, bvFTD is the most common type of FTD, estimated to account for more than half of all cases [12]. The prominent features include disinhibition, apathy/inertia, loss of empathy, compulsive behaviors, hyper-orality, and impaired executive function (***Table 2***) [13]. People with FTD may become socially withdrawn, inflexible, and impulsive. They may have a shortened attention span and a tendency to be easily distracted. Behavior may become socially inappropriate. People with bvFTD are usually unaware of the changes in their personality and behavior and the impact these changes have on others. Memory and visual-spatial functioning are initially relatively spared in bvFTD. Some individuals with bvFTD may develop symptoms similar to Parkinson disease, such as bradykinesia, rigidity, postural instability, and masked face.

LANGUAGE PRESENTATION

Nonfluent/Agrammatic Variant PPA

Nonfluent/agrammatic variant PPA, also referred to as progressive non-fluent aphasia (PNFA), accounts for about 25% of all FTD cases and involves problems with language expression [12]. People with nfvPPA have difficulty producing speech but retain the meaning of words and know what they want to say. As a result, speech may become hesitant, slow, and labored. Speech patterns may be "agrammatic" or "telegraphic," meaning that only the most important content words are used, without connecting words. For example, a patient might say "Tuesday...hospital...sister." Patients with nfvPPA have difficulty talking on the telephone and tend to talk progressively less. Eventually, some may become mute. While in the early stages, these patients continue to understand the speech of others, but this comprehension is eventually lost also. Reading and writing skills are better preserved than speech, although these abilities are also eventually lost. As the disease progresses, patients may develop behavioral symptoms. Some individuals with nfvPPA may develop extrapyramidal symptoms of rigidity and tremors, as seen in CBS and PSP.

Semantic Variant PPA

Semantic variant PPA, also referred to as semantic dementia, represents about 20% of FTD cases [12]. Semantic variant PPA involves the loss of understanding of the meaning of words and objects. Speech is still fluent and grammatically correct, but people with svPPA have a declining ability to comprehend the meaning of words (especially nouns) or to recognize familiar objects or faces. For example, a person with svPPA who is very familiar with vegetables might read a menu and ask: "What is broccoli?" If shown a picture of a carrot, the patient may not be able to name it and may not recognize the word when told. There are progressive word-finding problems, reading and spelling skills decline, and retrieving names becomes difficult. Later in the disease, people with svPPA may develop behavioral changes similar to those seen in patients with bvFTD.

Logopenic Variant PPA

Logopenic variant PPA is characterized by difficulty retrieving words, resulting in slow speech with frequent pauses. These patients may also have trouble repeating long phrases and understanding complex sentences. Eventually, people with lvPPA may become mute. Reading and writing skills are initially preserved, but these decline as the disease progresses. People with lvPPA have word-finding problems similar to people with AD and are often found to have AD pathology at autopsy [8].

For all patients with suspected language presentations of FTD, it is important to consider the role of culture and preferred language.

FTD OVERLAP WITH MOVEMENT DISORDERS

Progressive Supranuclear Palsy

PSP is a neurodegenerative condition characterized by problems with gait and balance, causing postural instability, falls, and difficulty with eye movement coordination. The pathophysiology of PSP shows a loss of cells in the basal ganglia, substantia nigra, subthalamus, and brainstem, and affected neurons have inclusions composed of abnormal tau protein. There are similarities between PSP and Parkinson disease, including bradykinesia, rigidity, masked face, dysarthria, dysphagia, apathy, and depression. Some people with PSP develop behavioral problems, but these are often milder than those seen in other types of FTD. Some people with PSP may develop progressive memory and language problems, and there may be a decline in executive function.

Corticobasal Syndrome

CBS is a neurodegenerative condition that may initially present with movement problems, dementia, or both. In CBS, there is atrophy in multiple areas of the brain, including the frontoparietal regions, basal ganglia, and cerebral peduncles. Neuronal inclusions are usually composed of abnormal tau protein. Signs of CBS typically begin with decreased movement on one side of the body, muscle rigidity, and tremor. A hand, arm, or leg on the affected side may demonstrate apraxia (i.e., inability to make the limb follow commands). Patients may describe the affected limb as not feeling like a part of their body, a sensation referred to as "alien limb syndrome." Symptoms may become bilateral as the disease progresses. People with CBS may also experience personality changes, executive dysfunction, and language problems as the disease progresses.

FTD with Motor Neuron Disease

Approximately 15% of people with FTD also develop problems with motor neurons that control voluntary movement [10]. This is referred to as FTD with motor neuron disease (FTD/MND) or FTD with amyotrophic lateral sclerosis (FTD/ALS). Pathologically, in addition to frontal and temporal lobe atrophy, there is also atrophy in the motor regions of the cortex and loss of motor neurons in the brain stem and spinal cord. In FTD/MND, damaged neurons usually have abnormal inclusions composed of the protein TDP-43. Patients may present with behavior or language problems, but then additionally develop muscle problems, including weakness, stiffness, twitches, cramps, and/or atrophy. Muscle problems can affect arms, legs, face, mouth, and tongue, causing patients to experience clumsiness, dysphagia, dysarthria, and hyper-reflexia. An estimated 15% of patients with MND or ALS go on to develop behavioral and executive dysfunction symptoms of FTD as their disease progresses [10].

CLINICAL DIAGNOSIS OF FTD

How do the early symptoms of FTD and Alzheimer disease differ?

The diagnosis of FTD can be challenging because of the wide range of symptoms, the relatively early age of onset, and the slow progression. There is no single test to diagnose FTD, and it may be initially misdiagnosed as a psychiatric disorder (e.g., depression, schizophrenia), AD, Parkinson disease, or vascular dementia. Accurate diagnosis of FTD is important because some of the medications used to treat these other diseases may be detrimental to patients with FTD. Patients with suspected FTD are often referred to neurologists or neuropsychologists with special expertise in FTD and related neurodegenerative disorders for a comprehensive evaluation.

The clinical diagnosis of FTD is based on the clinical history, family history, neurologic examination, neuropsychologic evaluation, and neuroimaging. Other tests may also be performed for differential diagnosis. The diagnostic process may take time, and the diagnosis may change as more tests are done or as new symptoms appear.

The clinical history is obtained from the patient and his/her family or friends. It is important that family or friends provide information regarding symptoms, as patients are often unaware of their behavior changes.

EARLY SIGNS AND SYMPTOMS OF FTD VERSUS ALZHEIMER DISEASE		
Clinical Features	**FTD**	**Alzheimer Disease**
Hallmark	Decline in behavior, language, and/or movement; memory is retained initially	Decline in memory; socially appropriate behavior is retained initially
Initial language problems	May involve speech production, understanding words and recognizing familiar objects, or retrieving words	Word-finding or name recall
Age at onset	Usually 45 to 64 years of age	Usually 65 years of age or older
Movement problems	May have early movement disorder, with gait and balance problems, rigidity, apraxia, or muscle weakness	Usually no movement problems early in disease
Source: [3; 8; 14]		*Table 3*

The family history should focus on whether any other relatives have had a neurodegenerative disease. Any cases of dementia, language problems, or movement disorders should be noted, along with specific information about symptoms, diagnosis, age of onset, course of disease, age at death, and autopsy findings. Such background information may be valuable for both diagnosis and understanding genetic risk.

The neurologic examination typically includes assessment of the patient's general appearance and speech, mental status, cranial nerves, motor system, sensation, reflexes, and cerebellar function (coordination and balance). Consulting a neurologist who has knowledge and experience in FTD can be valuable when reaching a definitive diagnosis.

The neuropsychologic examination assesses brain function and may identify areas of the brain that have been damaged. It typically involves an interview and the administration of written tests. These tests may focus on attention and concentration, memory, orientation, language, visual-spatial abilities, and/or executive functions (e.g., reasoning, planning, organizing, problem solving). Patients with FTD may show deterioration in the areas of attention and concentration, language, and executive function, but may do relatively well on memory and visual-spatial tests.

The Neuropsychiatric Inventory (NPI) may be administered to caregivers of patients with suspected FTD. This survey helps assess behavior and psychopathology by inquiring about the patient's delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, unusual motor activity, nighttime behavioral problems, and eating abnormalities.

Brain scans are important tools in the diagnosis of FTD. Computed tomography (CT) may be done to determine if there is a tumor, hemorrhage, or other brain injury that could account for the symptoms. Magnetic resonance imaging (MRI) provides better visualization of the brain than CT and is often done to evaluate brain atrophy when FTD is suspected. Patients with FTD have progressive frontal and anterior temporal atrophy apparent on MRI. Typically, in bvFTD, there is atrophy of the frontal lobe (involved in personality, judgment, and executive function) and the anterior temporal lobe. In nfvPPA, there is left frontal lobe atrophy (involved in speech production). In svPPA, the atrophy is focused in the anterior temporal lobe (involved in language and face recognition). In specialty or research centers, positron emission tomography (PET), single photon emission computed tomography (SPECT), or functional MRI (fMRI) brain scans may be done to further evaluate brain functioning.

While there is no laboratory test that can diagnose FTD, some tests may be ordered to rule out other diseases with symptoms similar to those of FTD. Blood work may be ordered to identify dehydration, thyroid disease, vitamin B12 deficiency, or infections affecting the brain. An electroencephalogram (EEG) may be done if there is concern that seizures might be causing the patient's symptoms. In the early stages of FTD, EEG findings are usually normal or have non-specific findings. Lumbar puncture may be done to evaluate cerebral spinal fluid and rule out rare brain infections or cancer. Electromyography may be used to identify muscle weakness or myoclonus if MND (or ALS) is being considered as a possible diagnosis. In addition, language evaluation by a speech pathologist can be an important tool in diagnosing patients with nonfluent/agrammatic, semantic, or logopenic variant PPA.

It may be challenging to clinically differentiate FTD from early AD (***Table 3***). The only way to establish an unquestionable diagnosis of FTD is through a brain autopsy after a patient has died. Examination of the brain tissue will show the precise location and severity of the brain atrophy, and microscopic studies can determine the protein composition of the inclusions in affected neurons.

For families, brain autopsy can confirm the diagnosis (or identify a different cause of the dementia) and bring a measure of closure. Accurate diagnosis may be especially important if there is concern about genetic risk to other family members.

Discussion about brain autopsy should be handled delicately and with compassion at a time that is appropriate for the family; the subject may be emotionally difficult for some families. Introducing the topic ahead of time allows families to consider their feelings about brain autopsy aside from the emotional crisis of the death of a loved one and the immediate time pressure of funeral arrangements. Families may then discuss the topic among themselves and come to a consensus.

Should a family wish to have a brain autopsy done when the patient dies, the physician can help identify a pathology service experienced in neurologic disorders and preliminary logistical planning can be done ahead of time. Arrangements may be coordinated with a research center that specializes in brain autopsy for FTD. The autopsy is done as soon as possible after death, often within 6 to 24 hours. The procedure is not disfiguring, so open-casket funerals may be planned if the family so chooses.

In addition to answering families' questions regarding diagnosis, brain autopsy can also aid researchers in better understanding the correlation between the clinical signs of FTD and the pathologic changes in the brain. This may benefit future generations by improving diagnosis and advancing research on therapies for FTD.

GENETICS AND FTD

If a parent carries a genetic mutation in the *MAPT* gene causing FTD, what is the risk to his/her child of inheriting the same genetic mutation?

Understanding of the role of genetics in FTD is still evolving. Presently, it appears that most cases of FTD (approximately 60%) are sporadic, meaning one person in a family has the disease, there is no family history of any relative with the disease, and the disease does not appear to be inherited.

However, approximately 40% of those with FTD report a family history of one or more relatives with a neurodegenerative disease [6; 9; 10]. This is referred to as familial FTD. In some cases of familial FTD, no specific genetic mutation can be identified as the cause. The risk to family members of a person with familial FTD without an identified genetic mutation is increased over the general population, but the specific increased risk is unclear.

An estimated 10% to 20% of all FTD cases are caused by an inherited genetic mutation [6; 8]. Patients with a strong family history of multiple relatives with FTD and/or MND are more likely to have an inherited form of FTD caused by a genetic mutation. Genetic mutations causing FTD are inherited in an autosomal dominant inheritance pattern, meaning each child of an affected parent is born with a 50% chance of inheriting the genetic mutation.

Several specific genetic mutations have been identified as being implicated in inherited FTD. In 1998, the first gene associated with hereditary FTD—the microtubule-associated protein tau (*MAPT*) gene on chromosome 17—was discovered [15; 16]. Mutations in this gene cause an abnormal accumulation of tau protein in affected neurons. *MAPT* mutations are thought to account for 2% to 11% of familial FTD cases [17]. These mutations most commonly cause bvFTD but may also cause svPPA, PSP, and/or CBS. FTD symptoms may vary widely, even within families.

In 2006, mutations in the progranulin (*GRN*) gene on chromosome 17 were discovered to cause FTD [18; 19]. Mutations in the *GRN* gene cause abnormal accumulations of TDP-43 protein in affected neurons. *GRN* mutations are thought to represent about 5% to 10% of all inherited FTD cases [17]. They most commonly cause bvFTD, but are also associated with nfvPPA and CBS. *GRN* mutations appear to have decreased penetrance, meaning that, for unknown reasons, some people with the mutation may not develop symptoms of the disease.

In 2011, the genetic mutation *C9orf72* was discovered on chromosome 9 [20; 21]. Mutations in *C9orf72* cause an abnormal accumulation of TDP-43 in affected neurons. To date, *C9orf72* mutations are the most common genetic cause of FTD, found in about 25% of familial FTD and 6% of sporadic cases [22]. *C9orf72* mutations appear to cause FTD (usually bvFTD or language presentation), MND, and a combination of FTD and MND.

Other very rare genetic mutations have also been associated with FTD. Mutations in the gene valosin-containing protein (VCP) on chromosome 9, charged multivesicular body protein 2B (CHMP2B) on chromosome 3, TAR DNA-binding protein (TARDBP), FUS, TBK1, EXT2, and SQSTM1 have been associated with FTD [29].

Clinical genetic testing is available for the *MAPT*, *GRN*, and *C9orf72* genetic mutations causing hereditary FTD, as well as some of the other very rare genetic mutations. Genetic testing may be ordered after informed consent and clear discussion of the implications with the patient and his/her family. For patients with FTD, identification of a genetic mutation confirms the diagnosis of FTD and provides information about risk to other family members. Each of the patient's siblings and each of the patient's children would be at 50/50 risk for having inherited the genetic mutation causing FTD. If a genetic mutation causing FTD is identified, other at-risk family members may be tested.

If a genetic mutation causing FTD is identified in a patient with FTD, unaffected at-risk family members could choose to have pre-symptomatic (predictive) genetic testing done to determine if they have inherited the genetic mutation that would someday cause FTD. Individuals considering pre-symptomatic genetic testing are referred for formal professional genetic counseling to help them make the best decision regarding whether or not to learn their FTD genetic status.

MANAGEMENT OF FTD

Which medications are approved for the treatment of FTD?

There is presently no treatment to slow the progression of or cure FTD. No medication has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of FTD; however, medications used to treat other disorders may be prescribed off-label for the management of FTD symptoms. Their use may be limited by the potential adverse effects. Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), may be prescribed for behavioral symptoms of FTD, and low-dose trazodone has been used for agitation and aggression [9]. While the anticholinesterase inhibitors donepezil, galantamine, and rivastigmine are beneficial for some patients with AD, they generally have not been helpful for patients with FTD [9]. The glutamate NMDA receptor antagonist memantine, used for moderate-to-severe AD, has been used for patients with FTD as well, but a 2013 study showed that it provided no benefit to patients with FTD and that it may be harmful to cognition [23]. Antipsychotics are occasionally used to treat significant agitation and behavioral symptoms, but only with caution, as antipsychotics can have serious adverse effects such as extrapyramidal adverse effects (parkinsonism), depression, sedation, falls, incontinence, and disinhibition, and patients with FTD may have an increased susceptibility to the these effects [9]. Elderly patients with dementia who take antipsychotics have a 1.6- to 1.7-fold increase in mortality secondary to cardiac problems or infection, prompting the FDA to issue a warning about their use in older patients with behavioral disturbances [9]. L-DOPA has shown a minimal response for parkinsonism in patients with PSP and CBD [28]. Research is being done to further evaluate the use of available medications for the management of FTD and to find new, more effective treatments.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Royal Australian and New Zealand College of Psychiatrists, general principles of dementia care apply for the management of frontotemporal dementia, but specific issues relate to the early onset of the illness in middle life and that affected persons may lack insight into their deficits leading to occupational and social problems.

(https://journals.sagepub.com/doi/abs/10.1177/1039856215582276. Last accessed October 15, 2021.)

Strength of Recommendation/Level of Evidence: Expert Opinion/Consensus Statement

Management of FTD includes providing care to patients with FTD and support to their families. Caring for a person with FTD involves managing the symptoms, keeping the patient safe, and providing help in activities of daily living.

Apathy is a common symptom in patients with bvFTD, often resulting in neglect of their personal hygiene and grooming. Supervision, encouragement, and help with bathing, dressing, and grooming may be needed. For behavioral problems, simple interventions like distraction (e.g., introducing a new activity) may help interrupt the troublesome behavior. For some patients, modification of the environment or behavior may help minimize the potential for harm. For example, if the patient is pacing, creating a safe route for him or her to walk can be helpful. Physical therapists may be able to help develop an exercise program to maintain mobility. Exercise has also been shown to improve mood and cognition and may improve behavior management in patients with dementia [24]. If behaviors such as agitation or aggression become severe, a medication may be prescribed off-label to control difficult or dangerous behaviors. Supervision may be necessary to ensure patients take medications as prescribed.

Some individuals with FTD have eating problems, such as overeating, eating just one type of food, or craving sweets. For these patients, it may be necessary to monitor weight and provide help with meal preparation to provide a balanced, nutritious diet. Access to additional foods, drinks, or sweets should be limited.

Speech pathologists or therapists may be helpful in diagnosing the specific language problems exhibited by patients with FTD, including nonfluent/agrammatic, semantic, or logopenic variant PPA. Speech therapy may also help patients to find new communication strategies, such as sign language, carrying cards with specific messages, or using a computer with pre-programmed words or phrases [25]. Such techniques may help those with language problems communicate with family and friends. Speech therapists may also be able to evaluate and address swallowing problems, if these arise.

Caring for a patient with FTD includes maintaining a safe environment for the patient and for those around him/her. A structured environment and keeping the daily routine the same is often helpful. In addition, persons with FTD should no longer drive, and safety measures should be taken at home, especially in the kitchen and bathroom. If a patient with FTD shows aggression, disinhibition, or poor judgment, close supervision is necessary when he/she is around others, especially children or the frail elderly, to prevent them from being inadvertently harmed.

It also may be necessary to monitor the patient's behavior in public places. If an individual displays inappropriate behavior, tense situations may be diffused by explaining that he or she has FTD and cannot control his/her behavior. Simple cards with this brief explanation can be made, carried, and shared with people who might be disturbed by a patient's inappropriate behavior.

If a patient with FTD has gait and balance problems, measures should be taken to prevent falls. This may include keeping the home environment free of obstacles and loose rugs and installing shower bars and a raised toilet seat. Mobility aids may be helpful. Occupational therapists should provide intervention to help patients with FTD complete activities of daily living as the disease progresses.

CAREGIVER SUPPORT

FTD places enormous burdens on the family. Most dementia care is provided at home by family caregivers, often spouses. Caregivers for those with FTD face physical, emotional, and financial challenges. FTD caregiver burden, stress, and depression are greater even than that seen with AD [26; 27].

The first challenge that families of those with FTD may face is obtaining an accurate diagnosis. The process can involve years of uncertainty and stress before the correct clinical diagnosis of FTD is made. Even during the diagnosis process, support for families begins with information and education about FTD. Accurate information can lead to understanding and a greater sense of control over the stressful situation. It is important for families and caregivers to understand that the behavior changes they observe are the result of the disease. Their loved one may display behaviors that are embarrassing, offensive, self-centered, uncaring, and aggressive, with complete lack of insight about how the behavior affects others. The caregiver may feel like he/she is suddenly living with a stranger.

The aggression, disinhibition, and poor judgment associated with FTD can put family members at risk of harm. Because FTD affects people at a relatively young age, there may still be children in the home. Families should recognize the risk to others in the home and seek help creating strategies to keep themselves and other family members safe.

Language may be impaired in people with FTD, making communication difficult. This can interfere not only with communication between the patient and the caregiver, but it can also limit participation in larger social activities. Speech therapy can provide new approaches to communication, helping not only the patient but also the caregiver.

Because FTD usually begins at a relatively young age, it can cause a significant financial burden for families. There may be loss of income, and retirement benefits may be affected because the patient is unable to continue working. Financial and legal issues that should be addressed include insurance, social security disability, financial planning for the future (when additional care will be needed), power-of-attorney arrangements, and a living will. Social workers, financial advisors, and attorneys are resources available to families to help address these issues.

The demands on caregivers increase as FTD progresses. Caregivers will be required to provide more supervision and increasing assistance for activities of daily living. While providing care for an individual with FTD, the caregiver may also be grieving the loss of his or her previously healthy loved one. Family caregivers can become physically and emotionally exhausted, and they may feel isolated in their role as caregiver. Interventions to help reduce caregiver stress include an individualized patient management plan, environmental changes to promote safety and facilitate care, and strengthening caregiver coping strategies and skills. Family caregivers should be encouraged to ask for and accept help in caring for their loved one with FTD, allowing them to take time for themselves and address their own health needs. Connection with community resources may also be helpful. Community resources for FTD caregivers include national organizations such as the Association for Frontotemporal Degeneration, attorneys and financial planners, social service programs, adult day care programs, respite care, support groups, and individual or family counseling.

Family caregivers should look ahead and consider how they wish care to be provided to their loved one as FTD progresses. Patients with FTD will become more dependent and more difficult to safely manage at home by a family caregiver as the disease progresses. Social workers can be a good resource to caregivers as they consider options such as extra in-home nursing care, care communities, and long-term care facilities. Locating an appropriate care facility that accepts patients with FTD

can be challenging. These patients are often younger, stronger, and more active than the typical residents of care facilities. Facility staff may need education and support to understand the unique features of FTD and to learn how to provide care to these patients while maintaining a safe environment for all residents in the facility.

Nurses play an important role in caring for those with FTD and providing support to their families. Nurses interact with patients with FTD and their families in the outpatient clinic setting, in-home care setting, and long-term care facility and may be involved in monitoring symptoms, developing and implementing individualized patient care plans, and providing direct patient care. It is important for all healthcare providers to coordinate care for the patient with FTD. All members of the interdisciplinary healthcare team can support families by listening to them, providing ongoing information and education about FTD, offering guidance to improve caregiving skills, and helping families connect to appropriate resources.

PROGRESSION OF FTD

The prognosis for people with FTD is poor. FTD worsens progressively, usually over several years, and patients require increasing behavioral supervision and personal care. Eventually, people with advanced FTD become mute and bedbound and require full care at home or in a care facility. As patients with FTD become more debilitated, they are vulnerable to complications such as infections and falls. The most common cause of death in people with FTD is infection (e.g., pneumonia) [3; 8]. The average duration of the disease is 6 to 13 years, but it can range from 2 to 20 years [3; 5].

RESEARCH RELATED TO FTD

What are the goals of research on FTD?

The goals for research on FTD include gaining a better understanding of the pathology; identifying causes and risk factors (genetic and environmental); improving the diagnosis of FTD through enhanced neuroimaging, biomarkers, and characterization of clinical features; developing therapies to treat, cure, or prevent FTD; and exploring new ways to support family caregivers. However, research on FTD is challenging. It is an uncommon disease, so awareness is low, there are fewer potential subjects available for research studies, and there is a relatively small market for medications. FTD is a complicated disease with a wide variety of presentations (behavior, language, and movement problems) and underlying causes (sporadic and genetic). Pathologically, microscopic brain inclusions may consist of different abnormal proteins (e.g., tau, TDP-43, FUS), but there are no good biomarkers to diagnose FTD or to monitor the progression of the disease. Drug development faces the challenge of creating a medication to treat FTD that can cross the blood/brain barrier.

Despite these challenges, the pace of research on FTD has accelerated rapidly. There are an increasing number of studies and a better awareness of the varied symptoms of FTD. In the past few decades, there have been discoveries of the genetic mutations underlying some causes of FTD and a growing understanding of the changes that occur in the brain of those with FTD. Presently, there are clinical trials underway for potential medications to treat FTD. Information on clinical research studies, including participation in studies, can be found at the National Institutes of Health website https://clinicaltrials.gov.

CASE STUDY

Patient A was a high school homecoming queen who completed two years of college, worked in an office, then married and had three children. She was an energetic homemaker and an active community volunteer, serving as school parent-teacher association president for several years, and was fastidious about her appearance.

Patient A's mother, three maternal uncles, a maternal grandfather, and great-grandmother died with dementia; her brother and maternal aunt are living with the disease. The mean age of onset of dementia in the family is 51 years, and the mean age at death is 67 years.

When Patient A is 52 years of age, her husband notices changes in her behavior. She often appears distracted, and her impeccable grooming declines. She is less affectionate toward him and she stops participating in community activities. She has difficulty making arrangements for a planned vacation. Her previously gourmet meals become simple, functional meals. She becomes obsessed with repeatedly raking the lawn, eventually killing all the grass in the yard. When her grandchildren visit, Patient A alternates between ignoring them and playing too rough. Patient A begins to impulsively leave the house for fast-paced walks, but she always returns home and never gets lost. She frequently visits a local shopping mall, getting down on her hands and knees looking for dropped change near the cash registers. She is once stopped by mall security for shoplifting. When shopping with her husband, she approaches strangers, stands inappropriately close to them, and announces "We don't know you."

Patient A's husband brings her to a dementia clinic for evaluation. A neurologic examination and neuropsychologic testing are completed. Memory and visual-spatial performance are in the normal range, but personality, judgment, and executive function show significant decline. A brain MRI shows frontal and anterior temporal lobe atrophy, and the diagnosis of familial bvFTD is made. Clinical genetic testing identifies a mutation in the *MAPT* gene on chromosome 17, the believed cause of the dementia.

Patient A's husband stops working in order to care for her at home. As her disease progresses, Patient A requires increasing care and supervision. She spends much of her day watching television, writing numbers in a notebook, and pacing. She develops a craving for sweets and often rummages through kitchen cabinets looking for candy. At mealtime, Patient A stuffs her mouth with food before chewing and swallowing properly, precipitating episodes of choking. She also develops a pattern of hand-clapping that she repeats every few minutes, along with the phrase "We haven't had any phone calls lately."

Patient A's husband is encouraged to accept help from others (such as their adult children), consider local adult day care programs, and utilize respite care at a nearby nursing home. He is in monthly phone contact with nursing staff to review symptoms and develop strategies for managing symptoms. At different times during her illness, Patient A is prescribed an antidepressant and an antipsychotic medication (off label) to treat difficult behavioral symptoms, but both were eventually discontinued. The family faces financial difficulties as a result of the husband's loss of income, diminished retirement benefits, and the later cost of nursing home care. Social work support helps the family address issues such as insurance, social security benefits, adult day care programs, and selecting a nursing facility for eventual long-term care.

When Patient A is 60 years of age, her husband is no longer able to care for her at home and she is admitted to a skilled nursing facility. She is incontinent and requires full care for all activities of daily living. Her husband visits twice daily, and she always appears to recognize him. That same year, Patient A dies unexpectedly of a myocardial infarction. A brain autopsy is done and confirms the diagnosis of FTD.

Patient A's husband shares the results of her genetic testing and autopsy with their three adult children. Each of Patient A's three children is at a 50% risk for having inherited the *MAPT* genetic mutation. Two of the children request pre-symptomatic genetic testing. The two children who request pre-symptomatic genetic testing are referred to professional genetic counselors. After genetic counseling, they both choose to have pre-symptomatic genetic testing done. One defers getting the results for two years, underscoring the very difficult personal decision it can be to choose pre-symptomatic genetic testing.

Patient A demonstrated the typical symptoms of bvFTD and her evaluation was done at a dementia center by specialists with expertise in FTD, so her initial diagnosis was strong. The neurologic evaluation, blood tests, neuropsychologic testing, and neuroimaging together led to the clinical diagnosis of bvFTD. Patient A's family history showed a pattern of autosomal dominant inheritance. The genetic cause of her FTD was confirmed by clinical genetic testing, which documented a mutation in the *MAPT* gene.

CONCLUSION

FTD is now recognized as one of the most common causes of dementia in persons younger than 65 years of age. This course has provided an overview of FTD epidemiology, pathophysiology, clinical presentation, diagnosis, management, prognosis, and current research. Understanding FTD can help healthcare professionals provide better care to patients with FTD and support to their families.

RESOURCES

Association for Frontotemporal Degeneration
2700 Horizon Drive, Suite 120
King of Prussia, PA 19406
(866) 507-7222
https://www.theaftd.org

National Institute on Aging
Building 31, Room 5C27
31 Center Drive, MSC 2292
Bethesda, MD 20892-2292
(800) 222-2225
https://www.nia.nih.gov

National Institute of Neurological Disorders and Stroke
P.O. Box 5801
Bethesda, MD 20824
(800) 352-9424
https://www.ninds.nih.gov

Customer Information/Evaluation insert located between pages 40–41.

Implicit Bias in Health Care

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

Course Objective
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.

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

1. Define implicit and explicit biases and related terminology.
2. Evaluate the strengths and limitations of the Implicit Association Test.
3. Describe how different theories explain the nature of implicit biases, and outline the consequences of implicit biases.
4. Discuss strategies to raise awareness of and mitigate or eliminate one's implicit biases.

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 appears at the end of this course.)

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

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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Designations of Credit
NetCE designates this continuing education activity for 3 ANCC contact hours.

This activity was planned by and for the healthcare team, and learners will receive 3 Interprofessional Continuing Education (IPCE) credits for learning and change.

AACN Synergy CERP Category B.

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

About the Sponsor

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

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

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

INTRODUCTION

In the 1990s, social psychologists Dr. Mahzarin Banaji and Dr. Tony Greenwald introduced the concept of implicit bias and developed the Implicit Association Test (IAT) as a measure. In 2003, the Institute of Medicine published the report *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care* highlighting the role of health professionals' implicit biases in the development of health disparities [1]. The phenomenon of implicit bias is premised on the assumption that while well-meaning individuals may deny prejudicial beliefs, these implicit biases negatively affect their clinical communications, interactions, and diagnostic and treatment decision-making [2; 3].

One explanation is that implicit biases are a heuristic, or a cognitive or mental shortcut. Heuristics offer individuals general rules to apply to situations in which there is limited, conflicting, or unclear information. Use of a heuristic results in a quick judgment based on fragments of memory and knowledge, and therefore, the decisions made may be erroneous. If the thinking patterns are flawed, negative attitudes can reinforce stereotypes [4]. In health contexts, this is problematic because clinical judgments can be biased and adversely affect health outcomes. The Joint Commission provides the following example [3]: A group of physicians congregate to examine a child's x-rays but has not been able to reach a diagnostic consensus. Another physician with no knowledge of the case is passing by, sees the x-rays, and says "Cystic fibrosis." The group of physicians was aware that the child is African American and had dismissed cystic fibrosis because it is less common among Black children than White children.

The purpose of this course is to provide health professionals an overview of implicit bias. This includes an exploration of definitions of implicit and explicit bias. The nature and dynamics of implicit biases and how they can affect health outcomes will be discussed. Finally, because implicit biases are unconscious, strategies will be reviewed to assist in raising professionals' awareness of and interventions to reduce them.

DEFINITIONS OF IMPLICIT BIAS AND OTHER TERMINOLOGIES

IMPLICIT VS. EXPLICIT BIAS

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 [5]. 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 [6]. 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 [2; 7; 8; 9]. Some have asserted that the cognitive processes that dictate implicit and explicit biases are separate and independent [9].

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 [10]. 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 [11]. According to Georgetown University's National Center on Cultural Competency, social characteristics that can trigger implicit biases include [12]:

- Age
- Disability
- Education
- English language proficiency and fluency
- Ethnicity
- Health status
- Disease/diagnosis (e.g., HIV/AIDS)
- 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 [6; 13]. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages [13].

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 [2].

OTHER COMMON TERMINOLOGIES

In addition to understanding implicit and explicit bias, there is additional terminology related to these concepts that requires specific definition.

Cultural Competence

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 [14]. 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

What is 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 [15]. Cultural humility is a lifelong process involving reflexivity, self-evaluation, and self-critique [16].

Discrimination

Discrimination has traditionally been viewed as the outcome of prejudice [17]. It encompasses overt or hidden actions, behaviors, or practices of members in a dominant group against members of a subordinate group [18]. Discrimination has also been further categorized as lifetime discrimination, which consists of major discreet discriminatory events, or everyday discrimination, which is subtle, continual, and part of day-to-day life and can have a cumulate effect on individuals [19].

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" [20]. Diversity is often conceptualized into singular dimensions as opposed to multiple and intersecting diversity factors [21].

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 [22].

Prejudice

Prejudice is a generally negative feeling, attitude, or stereotype against members of a group [23]. 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" [23]. Prejudice stems from the process of ascribing every member of a group with the same attribute [24].

Race

Race is linked to biology. Race is partially defined by physical markers (e.g., skin or hair color) and is generally used as a mechanism for classification [25]. It does not refer to cultural institutions or patterns. In modern history, skin color has been used to classify people and to imply that there are distinct biologic differences within human populations [26]. Historically, the U.S. Census has defined race according to ancestry and blood quantum; today, it is based on self-classification [26].

There are scholars who assert that race is socially constructed without any biological component [27]. For example, racial characteristics are also assigned based on differential power and privilege, lending to different statuses among groups [28].

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" [29]. 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 [30]. 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 [31; 32].

MEASUREMENT OF IMPLICIT BIAS: A FOCUS ON THE IAT

What tool is used to quantitatively measure implicit bias?

Project Implicit is a research project sponsored by Harvard University and devoted to the study and monitoring of implicit biases. It houses the Implicit Association Test (IAT), which is one of the most widely utilized standardized instruments to measure implicit biases. The IAT is based on the premise that implicit bias is an objective and discreet phenomenon that can be measured in a quantitative manner. Developed and first introduced in 1998, it is an online test that assesses implicit bias by measuring how quickly people make associations between targeted categories with a list of adjectives [33]. For example, research participants might be assessed for their implicit biases by seeing how rapidly they make evaluations among the two groups/categories career/family and male/female. Participants tend to more easily affiliate terms for which they hold implicit or explicit biases. So, unconscious biases are measured by how quickly research participants respond to stereotypical pairings (e.g., career/male and family/female). The larger the difference between the individual's performance between the two groups, the stronger the degree of bias [34; 35]. Since 2006, more than 4.6 million individuals have taken the IAT, and results indicate that the general population holds implicit biases [3].

interactive activity

Visit https://implicit.harvard.edu/implicit and complete an assessment. Does it reflect your perception of your own biases? Did you learn anything about yourself?

Measuring implicit bias is complex, because it requires an instrument that is able to access underlying unconscious processes. While many of the studies on implicit biases have employed the IAT, there are other measures available. They fall into three general categories: the IAT and its variants, priming methods, and miscellaneous measures, such as self-report, role-playing, and computer mouse movements [36]. This course will focus on the IAT, as it is the most commonly employed instrument.

The IAT is not without controversy. One of the debates involves whether IAT scores focus on a cognitive state or if they reflect a personality trait. If it is the latter, the IAT's value as a diagnostic screening tool is diminished [37]. There is also concern with its validity in specific arenas, including jury selection and hiring [37]. Some also maintain that the IAT is sensitive to social context and may not accurately predict behavior [37]. Essentially, a high IAT score reflecting implicit biases does not necessarily link to discriminating behaviors, and correlation should not imply causation. A meta-analysis involving 87,418 research participants found no evidence that changes in implicit biases affected explicit behaviors [38].

EXTENT OF IMPLICIT BIASES AND RISK FACTORS

Among the more than 4 million participants who have completed the IAT, individuals generally exhibited implicit preference for White faces over Black or Asian faces. They also held biases for light skin over dark skin, heterosexual over gender and sexual minorities (LGBTQ+), and young over old [39]. The Pew Research Center also conducted an exploratory study on implicit biases, focusing on the extent to which individuals adhered to implicit racial biases [40]. A total of 2,517 IATs were completed and used for the analysis. Almost 75% of the respondents exhibited some level of implicit racial biases. Only 20% to 30% did not exhibit or showed very little implicit bias against the minority racial groups tested. Approximately half of all single-race White individuals displayed an implicit preference for White faces over Black faces. For single-race Black individuals, 45% had implicit preference for their own group. For biracial White/Black adults, 23% were neutral. In addition, 22% of biracial White/Asian participants had no or

minimal implicit racial biases. However, 42% of the White/Black biracial adults leaned toward a pro-White bias.

In another interesting field experiment, although not specifically examining implicit bias, resumes with names commonly associated with African American or White candidates were submitted to hiring officers [41]. Researchers found that resumes with White-sounding names were 50% more likely to receive callbacks than resumes with African American-sounding names [41]. The underlying causes of this gap were not explored.

Implicit bias related to sex and gender is also significant. A survey of emergency medicine and obstetrics/gynecology residency programs in the United States sought to examine the relationship between biases related to perceptions of leadership and gender [42]. In general, residents in both programs (regardless of gender) tended to favor men as leaders. Male residents had greater implicit biases compared with their female counterparts.

Other forms of implicit bias can affect the provision of health and mental health care. One online survey examining anti-fat biases was provided to 4,732 first-year medical students [43]. Respondents completed the IAT, two measures of explicit bias, and an anti-fat attitudes instrument. Nearly 75% of the respondents were found to hold implicit anti-fat biases. Interestingly, these biases were comparable to the scope of implicit racial biases. Male sex, non-Black race, and lower body mass index (BMI) predicted holding these implicit biases.

Certain conditions or environmental risk factors are associated with an increased risk for certain implicit biases, including [44; 45]:

- 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

THEORETIC EXPLANATIONS AND CONTROVERSIES

A variety of theoretical frameworks have been used to explore the causes, nature, and dynamics of implicit biases. Each of the theories is described in depth, with space given to explore controversies and debates about the etiology of implicit bias.

SOCIAL PSYCHOLOGICAL AND COGNITIVE THEORETICAL FRAMEWORKS

One of the main goals of social psychology is to understand how attitudes and belief structures influence behaviors. Based on frameworks from both social and cognitive psychology, many theoretical frameworks used to explain implicit bias revolve around the concept of social cognition. One branch of cognitive theory focuses on the role of implicit or nondeclarative memory. Experts believe that this type of memory allows certain behaviors to be performed with very little conscious awareness or active thought. Examples include tooth brushing, tying shoelaces, and even driving. To take this concept one step farther, implicit memories may also underlie social attitudes and stereotype attributions [46]. This is referred to as implicit social cognition. From this perspective, implicit biases are automatic expressions based on belonging to certain social groups [47]. The IAT is premised on the role of implicit memory and past experiences in predicting behavior without explicit memory triggering [48].

Another branch of cognitive theory used to describe implicit biases involves heuristics. When quick decisions are required under conditions of uncertainty or fatigue, and/or when there is a tremendous amount of information to assimilate without sufficient time to process, decision-makers resort to heuristics [49]. Heuristics are essentially mental short cuts that facilitate (usually unconscious) rules that promote automatic processing [50]. However, these rules can also be influenced by socialization factors, which could then affect any unconscious or latent cognitive associations about power, advantage, and privilege. Family, friends, media, school, religion, and other social institutions all play a role in developing and perpetuating implicit and explicit stereotypes, and cognitive evaluations can be primed or triggered by an environmental cue or experience [51]. When a heuristic is activated, an implicit memory or bias may be triggered simultaneously [47]. This is also known as the dual-process model of information processing [50].

BEHAVIORAL OR FUNCTIONAL PERSPECTIVES

Behavioral or functional theorists argue that implicit bias is not necessarily a latent or unconscious cognitive structure. Instead, this perspective recognizes implicit bias as a group-based behavior [52]. Behavior is biased if it is influenced by social cues indicating the social group to which someone belongs [52]. Social cues can occur rapidly and unintentionally, which ultimately leads to automatic or implicit effects on behavior. The appeal of a behavioral or functional approach to implicit bias is that it is amoral; that is, it is value- and judgment-free [52]. Rather than viewing implicit bias as an invisible force (i.e., unconscious cognitive structure), it is considered a normal behavior [53].

NEUROSCIENTIFIC PERSPECTIVES

Implicit bias has neuroscientific roots as well and has been linked to functions of the amygdala [2; 54]. The amygdala is located in the temporal lobe of the brain, and it communicates with the hypothalamus and plays a large role in memory. When

situations are emotionally charged, the amygdala is activated and connects the event to memory, which is why individuals tend to have better recall of emotional events. This area of the brain is also implicated in processing fear. Neuroscientific studies on implicit biases typically use functional magnetic resonance imaging (fMRI) to visualize amygdala activation during specific behaviors or events. In experimental studies, when White research subjects were shown photos of Black faces, their amygdala appeared to be more activated compared to when they viewed White faces [55]. This trend toward greater activation when exposed to view the faces of persons whose race differs from the viewer starts in adolescence and appears to increase with age [54]. This speaks to the role of socialization in the developmental process [54].

It may be that the activation of the amygdala is an evolutionary threat response to an outgroup [56]. Another potential explanation is that the activation of the amygdala is due to the fear of appearing prejudiced to others who will disapprove of the bias [56]. The neuroscientific perspective of implicit bias is controversial. While initial empirical studies appear to link implicit bias to amygdala activation, many researchers argue this relationship is too simplistic [2].

STRUCTURAL OR CRITICAL THEORY

How might critical theory or a structural perspective be integrated into the values and ethics of interprofessional collaboration and practice?

Many scholars and policymakers are concerned about the narrow theoretical views that researchers of implicit bias have taken. By focusing on unconscious cognitive structures, social cognition and neuroscientific theories miss the opportunity to also address the role of macro or systemic factors in contributing to health inequities [9; 57]. By focusing on the neurobiology of implicit bias, for example, racism and bias is attributed to central nervous system function, releasing the individual from any control or responsibility. However, the historical legacy of prejudice and bias has roots in economic and structural issues that produce inequities [58]. Larger organizational, institutional, societal, and cultural forces contribute, perpetuate, and reinforce implicit and explicit biases, racism, and discrimination. Psychological and neuroscientific approaches ultimately decontextualize racism [9; 57].

In response to this conflict, a systems-based practice has been proposed [59]. This type of practice emphasizes the role of sociocultural determinants of health outcome and the fact that health inequities stem from larger systemic forces. As a result, medical and health education and training should focus on how patients' health and well-being may reflect structural vulnerabilities driven in large part by social, cultural, economic, and institutional forces. Health and mental health professionals also require social change and advocacy skills to ensure that they can effect change at the organizational and institutional levels [59].

Implicit bias is not a new topic; it has been discussed and studied for decades in the empirical literature. Because implicit bias is a complex and multifaceted phenomenon, it is important to recognize that there may be no one single theory that can fully explain its etiology.

CONSEQUENCES OF IMPLICIT BIASES

HEALTH DISPARITIES

Implicit bias has been linked to a variety of health disparities [1]. Health disparities are differences in health status or disease that systematically and adversely affect less advantaged groups [60]. These inequities are often linked to historical and current unequal distribution of resources due to poverty, structural inequities, insufficient access to health care, and/or environmental barriers and threats [61]. Healthy People 2030 defines a health disparity as [62]:

> ...a particular type of health difference that is closely linked with social, economic, and/or environmental disadvantage. Health disparities adversely affect groups of people who have systematically experienced greater obstacles to health based on their racial or ethnic group; religion; socioeconomic status; gender; age; mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion.

As noted, in 2003, the Institute of Medicine implicated implicit bias in the development and continued health disparities in the United States [1]. Despite progress made to lessen the gaps among different groups, health disparities continue to exist. One example is racial disparities in life expectancy among Black and White individuals in the United States. Life expectancy for Black men is 4.4 years lower than White men; for Black women, it is 2.9 years lower compared with White women [63]. Hypertension, diabetes, and obesity are more prevalent in non-Hispanic Black populations compared with non-Hispanic White groups (25%, 49%, and 59% higher, respectively) [64]. In one study, African American and Latina women were more likely to experience cesarean deliveries than their White counterparts, even after controlling for medically necessary procedures [65]. This places African American and Latina women at greater risk of infection and maternal mortality.

Gender health disparities have also been demonstrated. Generally, self-rated physical health (considered one of the best proxies to health) is poorer among women than men. Depression is also more common among women than men [66]. Lesbian and bisexual women report higher rates of depression and are more likely than non-gay women to engage risk behaviors such as smoking and binge drinking, perhaps as a result of LGBTQ+-related stressors. They are also less likely to access healthcare services [67].

Socioeconomic status also affects health care engagement and quality. In a study of patients seeking treatment for thoracic trauma, those without insurance were 1.9 times more likely to die compared with those with private insurance [68].

CLINICAL DECISIONS AND PROVIDER-PATIENT INTERACTIONS

In an ideal situation, health professionals would be explicitly and implicitly objective and clinical decisions would be completely free of bias. However, healthcare providers have implicit (and explicit) biases at a rate comparable to that of the general population [6; 69]. It is possible that these implicit biases shape healthcare professionals' behaviors, communications, and interactions, which may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions [69]. They may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up [7].

In a landmark 2007 study, a total of 287 internal medicine physicians and medical residents were randomized to receive a case vignette of an either Black or White patient with coronary artery disease [70]. All participants were also administered the IAT. When asked about perceived level of cooperativeness of the White or Black patient from the vignette, there were no differences in their explicit statements regarding cooperativeness. Yet, the IAT scores did show differences, with scores showing that physicians and residents had implicit preferences for the White patients. Participants with greater implicit preference for White patients (as reflected by IAT score) were more likely to select thrombolysis to treat the White patient than the Black patient [70]. This led to the possible conclusion that implicit racial bias can influence clinical decisions regarding treatment and may contribute to racial health disparities. However, some argue that using vignettes depicting hypothetical situations does not accurately reflect real-life conditions that require rapid decision-making under stress and uncertainty.

PATIENTS' PERCEPTIONS OF CARE

It has been hypothesized that providers' levels of bias affect the ratings of patient-centered care [34]. Patient-centered care has been defined as patients' positive ratings in the areas of perception of provider concern, provider answering patients' questions, provider integrity, and provider knowledge of the patient. Using data from 134 health providers who completed the IAT, a total of 2,908 diverse racial and ethnic minority patients participated in a telephone survey. Researchers found that for providers who scored high on levels of implicit bias, African American patients' ratings for all dimensions of patient-centered care were low compared with their White patient counterparts. Latinx patient ratings were low regardless of level of implicit bias.

A 2013 study recorded clinical interactions between 112 low-income African American patients and their 14 non-African American physicians for approximately two years [71]. Providers' implicit biases were also assessed using the IAT. In general, the physicians talked more than the patients; however, physicians with higher implicit bias scores also had a higher ratio of physician-to-patient talk time. Patients with higher levels of perceived discrimination had a lower ratio of physician-to-patient talk time (i.e., spoke more than those with lower reported perceived discrimination). A lower ratio of physician-patient talk time correlated to decreased likelihood of adherence.

Another study assessed 40 primary care physicians and 269 patients [72]. The IAT was administered to both groups, and their interactions were recorded and observed for verbal dominance (defined as the time of physician participation relative to patient participation). When physicians scored higher on measures of implicit bias, there was 9% more verbal dominance on the part of the physicians in the visits with Black patients and 11% greater in interactions with White patients. Physicians with higher implicit bias scores and lower verbal dominance also received lower scores on patient ratings on interpersonal care, particularly from Black patients [72].

In focus groups with racially and ethnically diverse patients who sought medical care for themselves or their children in New York City, participants reported perceptions of discrimination in health care [73]. They reported that healthcare professionals often made them feel less than human, with varying amounts of respect and courtesy. Some observed differences in treatment compared with White patients. One Black woman reported [73]:

> When the doctor came in [after a surgery], she proceeded to show me how I had to get up because I'm being released that day "whether I like it or not"... She yanked the first snap on the left leg...So I'm thinking, 'I'm human!' And she was courteous to the White lady [in the next bed], and I've got just as much age as her. I qualify on the level and scale of human being as her, but I didn't feel that from the doctor.

Another participant was a Latino physician who presented to the emergency department. He described the following [73]:

> They put me sort of in the corner [in the emergency department] and I can't talk very well because I can't breathe so well. The nurse comes over to me and actually says, "Tu tiene tu Medicaid?" I whispered out, "I'm a doctor...and I have insurance." I said it in perfect English. Literally, the color on her face went completely white...Within two minutes there was an orthopedic team around me...I kept wondering about what if I hadn't been a doctor, you know? Pretty eye opening and very sad.

These reports are illustrative of many minority patients' experiences with implicit and explicit racial/ethnic biases. Not surprisingly, these biases adversely affect patients' views of their clinical interactions with providers and ultimately contribute to their mistrust of the healthcare system.

DEVELOPMENTAL MODEL TO RECOGNIZING AND REDUCING IMPLICIT BIAS

There are no easy answers to raising awareness and reducing health providers' implicit bias. Each provider may be in a different developmental stage in terms of awareness, understanding, acceptance, and application of implicit bias to their practice. A developmental model for intercultural sensitivity training has been established to help identify where individuals may be in this developmental journey [74; 75]. It is important to recognize that the process of becoming more self-aware is fluid; reaching one stage does not necessarily mean that it is "conquered" or that there will not be additional work to do in that stage. As a dynamic process, it is possible to move back and forth as stress and uncertainty triggers implicit biases [74]. This developmental model includes six stages:

- Denial: In this stage, the individual has no awareness of the existence of cultural differences between oneself and members of other cultural groups and subgroups. Individuals in this stage have no awareness of implicit bias and cannot distinguish between explicit and implicit biases.
- Defense: In this stage, the person may accept that implicit biases exist but does not acknowledge that implicit biases exist within themselves.
- Minimization: An individual in this stage acknowledges that implicit biases may exist in their colleagues and possibly themselves. However, he or she is uncertain of their consequences and adverse effects. Furthermore, the person believes he or she is able to treat patients in an objective manner.
- Acceptance: In the acceptance stage, the individual recognizes and acknowledges the role of implicit biases and how implicit biases influence interactions with patients.
- Adaptation: Those in the adaptation stage self-reflect and acknowledge that they have unrecognized implicit biases. Not only is there an acknowledgement of the existence of implicit bias, these people begin to actively work to reduce the potential impact of implicit biases on interactions with patients.
- Integration: At this stage, the health professional works to incorporate change in their day-to-day practice in order to mitigate the effects of their implicit biases on various levels—from the patient level to the organization level.

CREATING A SAFE ENVIRONMENT

If psychological safety is threatened, what might be a potential outcome in implicit bias training?

Creating a safe environment is the essential first step to exploring issues related to implicit bias. Discussions of race, stereotypes, privilege, and implicit bias, all of which are very complex, can be volatile or produce heightened emotions. When individuals do not feel their voices are heard and/or valued, negative emotions or a "fight-or-flight" response can be triggered [76]. This may manifest as yelling, demonstrations of anger, or crying or leaving the room or withdrawing and remaining silent [76].

Creating and fostering a sense of psychological safety in the learning environment is crucial. Psychological safety results when individuals feel that their opinions, views, thoughts, and contributions are valued despite tension, conflict, and discomfort. This allows the individual to feel that their identity is intact [76]. When psychological safety is threatened, individuals' energies are primarily expended on coping rather than learning [76]. As such, interventions should not seek to confront individuals or make them feel guilty and/or responsible [77].

When implicit bias interventions or assessments are planned, facilitators should be open, approachable, non-threatening, and knowledgeable; this will help create a safe and inclusive learning environment [77]. The principles of respect, integrity, and confidentiality should be communicated [77]. Facilitators who demonstrate attunement, authenticity, and power-sharing foster positive and productive dialogues about subjects such as race and identity [76]. Attunement is the capacity of an individual to tacitly comprehend the lived experiences of others, using their perspectives to provide an alternative viewpoint for others. Attunement does not involve requiring others to talk about their experiences if they are not emotionally ready [76]. Authenticity involves being honest and transparent with one's own position in a racialized social structure and sharing one's own experiences, feelings, and views. Being authentic also means being vulnerable [76]. Finally, power-sharing entails redistributing power in the learning environment. The education environment is typically hierarchical, with an expert holding more power than students or participants. Furthermore, other students may hold more power by virtue of being more comfortable speaking/interacting [76]. Ultimately, promoting a safe space lays a foundation for safely and effectively implementing implicit bias awareness and reduction interventions.

STRATEGIES TO PROMOTE AWARENESS OF IMPLICIT BIAS

As discussed, the IAT can be used as a metric to assess professionals' level of implicit bias on a variety of subjects, and this presupposes that implicit bias is a discrete phenomenon that can be measured quantitatively [79]. When providers are aware that implicit biases exist, discussion and education can be implemented to help reduce them and/or their impact.

Another way of facilitating awareness of providers' implicit bias is to ask self-reflective questions about each interaction with patients. Some have suggested using SOAP (subjective, objective, assessment, and plan) notes to assist practitioners in identifying implicit biases in day-to-day interactions with patients [80]. Integrating the following questions into charts and notes can stimulate reflection about implicit bias globally and for each specific patient interaction:

- Did I think about any socioeconomic and/or environmental factors that may contribute to the health and access of this patient?
- How was my communication and interaction with this patient? Did it change from my customary pattern?
- How could my implicit biases influence care for this patient?

When reviewing the SOAP notes, providers can look for recurring themes of stereotypical perceptions, biased communication patterns, and/or types of treatment/interventions proposed and assess whether these themes could be influenced by biases related to race, ethnicity, age, gender, sexuality, or other social characteristics.

A review of empirical studies conducted on the effectiveness of interventions promoting implicit bias awareness found mixed results. At times, after a peer discussion of IAT scores, participants appeared less interested in learning and employing implicit bias reduction interventions. However, other studies have found that receiving feedback along with IAT scores resulted in a reduction in implicit bias [81]. Any feedback, education, and discussions should be structured to minimize participant defensiveness [81].

INTERVENTIONS TO REDUCE IMPLICIT BIASES

Interventions or strategies designed to reduce implicit bias may be further categorized as change-based or control-based [58]. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors [58]. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

PERSPECTIVE TAKING

Perspective taking is a strategy of taking on a first-person perspective of a person in order to control one's automatic response toward individuals with certain social characteristics that might trigger implicit biases [82]. The goal is to increase psychological closeness, empathy, and connection with members of the group [4]. Engaging with media that presents a perspective (e.g., watching documentaries, reading an autobiography) can help promote better understanding of the specific group's lives, experiences, and viewpoints. In one study, participants who adopted the first-person perspectives of African Americans had more positive automatic evaluations of the targeted group [83].

interactive activity

Consuming media that presents a viewpoint and life experience different from your own can help minimize implicit biases. Visit the following sites and consider how they might challenge or expand your perception of each group. Internet searches can help identify many more options for various social groups.

Think Out Loud Podcast
Young Black people share their experiences growing up in Portland, Oregon.
https://www.opb.org/article/2020/10/30/young-black-people-share-their-experiences-growing-up-in-portland

George Takei: Growing Up Asian-American
This PBS clip is a brief introduction, and the subject can be further explored in Takei's book *They Called Us Enemy*.
https://www.pbs.org/wnet/pioneers-of-television/video/george-takei-growing-up-asian-american

Seattle Public Library LGBTQ Staff Picks
A reading list including books and films focusing on LGBTQ+ life, culture, history, and politics.
https://www.spl.org/programs-and-services/social-justice/lgbtq/lgbt-staff-picks

EMPATHY INTERVENTIONS

Promoting positive emotions such as empathy and compassion can help reduce implicit biases. This can involve strategies like perspective taking and role playing [77]. In a study examining analgesic prescription disparities, nurses were shown photos of White or African American patients exhibiting pain and were asked to recommend how much pain medication was

needed; a control group was not shown photos. Those who were shown images of patients in pain displayed no differences in recommended dosage along racial lines; however, those who did not see the images averaged higher recommended dosages for White patients compared with Black patients [84]. This suggests that professionals' level of empathy (enhanced by seeing the patient in pain) affected prescription recommendations.

In a study of healthcare professionals randomly assigned to an empathy-inducing group or a control group, participants were given the IAT to measure implicit bias prior to and following the intervention. Level of implicit bias among participants in the empathy-inducing group decreased significantly compared with their control group counterparts [85].

INDIVIDUATION

Individuation is an implicit bias reduction intervention that involves obtaining specific information about the individual and relying on personal characteristics instead of stereotypes of the group to which he or she belongs [4; 82]. The key is to concentrate on the person's specific experiences, achievements, personality traits, qualifications, and other personal attributes rather than focusing on gender, race, ethnicity, age, ability, and other social attributes, all of which can activate implicit biases. When providers lack relevant information, they are more likely to fill in data with stereotypes, in some cases unconsciously. Time constraints and job stress increase the likelihood of this occurring [69].

MINDFULNESS

Mindfulness requires stopping oneself and deliberately emptying one's mind of distractions or allowing distractions to drift through one's mind unimpeded, focusing only on the moment; judgment and assumptions are set aside. This approach involves regulating one's emotions, responses, and attention to return to the present moment, which can reduce stress and anxiety [86]. There is evidence that mindfulness can help regulate biological and emotional responses and can have a positive effect on attention and habit formation [4]. A mindfulness activity assists individuals to be more aware of their thoughts and sensations. This focus on deliberation moves the practitioner away from a reliance on instincts, which is the foundation of implicit bias-affected practice [4; 87].

Mindfulness approaches include yoga, meditation, and guided imagery. Additional resources to encourage a mindfulness practice are provided later in this course.

An approach to mindfulness using the acronym STOPP has been developed as a practical exercise to engage in mindfulness in any moment. STOPP is an acronym for [88]:

- Stop
- Take a breath
- Observe
- Pull back
- Practice

interactive activity

Visit the following website to view a short, animated video on the STOPP technique. After viewing the video, consider how you can incorporate the technique into your work.

https://www.youtube.com/watch?v=tStXi7f7Vgk

Mindfulness practice has been explored as a technique to reduce activation or triggering of implicit bias, enhance awareness of and ability to control implicit biases that arise, and increase capacity for compassion and empathy toward patients by reducing stress, exhaustion, and compassion fatigue [89]. One study examined the effectiveness of a loving-kindness meditation practice training in improving implicit bias toward African Americans and unhoused persons. One hundred one non-Black adults were randomized to one of three groups: a six-week loving-kindness mindfulness practice, a six-week loving-kindness discussion, or the waitlist control. The IAT was used to measure implicit biases, and the results showed that the loving-kindness meditation practice decreased levels of implicit biases toward both groups [90].

There is also some novel evidence that mindfulness may have neurologic implications. For example, one study showed decreased amygdala activation after a mindfulness meditation [91]. However, additional studies are required in this area before conclusions can be reached.

COUNTER-STEREOTYPICAL IMAGING

Counter-stereotypical imaging approaches involve presenting an image, idea, or construct that is counter to the oversimplified stereotypes typically held regarding members of a specific group. In one study, participants were asked to imagine either a strong woman (the experimental condition) or a gender-neutral event (the control condition) [92]. Researchers found that participants in the experimental condition exhibited lower levels of implicit gender bias. Similarly, exposure to female leaders was found to reduce implicit gender bias [93]. Whether via increased contact with stigmatized groups to contradict prevailing stereotypes or simply exposure to counter-stereotypical imaging, it is possible to unlearn associations underlying various implicit biases. If the social environment is important in priming positive evaluations, having more positive visual images of members in stigmatized groups can help reduce implicit biases [94]. Some have suggested that even just hanging photos and having computer screensavers reflecting positive images of various social groups could help to reduce negative associations [94].

EFFECTIVENESS OF IMPLICIT BIAS INTERVENTIONS

The effectiveness of implicit bias trainings and interventions has been scrutinized. In a 2019 systematic review, different types of implicit bias reduction interventions were evaluated. A meta-analysis of empirical studies published between May 2005 and April 2015 identified eight different classifications of interventions [13]:

- Engaging with others' perspectives, consciousness-raising, or imagining contact with outgroup: Participants either imagine how the outgroup thinks and feels, imagine having contact with the outgroup, or are made aware of the way the outgroup is marginalized or given new information about the outgroup.
- Identifying the self with the outgroup: Participants perform tasks that lessen barriers between themselves and the outgroup.
- Exposure to counter-stereotypical exemplars: Participants are exposed to exemplars that contradict negative stereotypes of the outgroup.
- Appeal to egalitarian values: Participants are encouraged to activate egalitarian goals or think about multiculturalism, cooperation, or tolerance.
- Evaluative conditioning: Participants perform tasks to strengthen counter-stereotypical associations.
- Inducing emotion: Emotions or moods are induced in participants.
- Intentional strategies to overcome biases: Participants are instructed to implement strategies to over-ride or suppress their biases.
- Pharmacotherapy

Interventions found to be the most effective were, in order from most to least, [13]:

- Intentional strategies to overcome biases
- Exposure to counter-stereotypical exemplars
- Identifying self with the outgroup
- Evaluative conditioning
- Inducing emotions

In general, the sample sizes were small. It is also unclear how generalizable the findings are, given many of the research participants were college psychology students. The 30 studies included in the meta-analysis were cross-sectional (not longitudinal) and only measured short-term outcomes, and there is some concern about "one shot" interventions, given the fact that implicit biases are deeply embedded. Would simply acknowledging the existence of implicit biases be sufficient to eliminate them [95; 96]? Or would such a confession act as an illusion to having self-actualized and moved beyond the bias [95]?

Optimally, implicit bias interventions involve continual practice to address deeply habitual implicit biases or interventions that target structural factors [95; 96].

ROLE OF INTERPROFESSIONAL COLLABORATION AND PRACTICE AND IMPLICIT BIASES

The study of implicit bias is appropriately interdisciplinary, representing social psychology, medicine, health psychology, neuroscience, counseling, mental health, gerontology, LGBTQ+ studies, religious studies, and disability studies [13]. Therefore, implicit bias empirical research and curricula training development lends itself well to interprofessional collaboration and practice (ICP).

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 [97]. ICP also involves the sharing of roles, responsibilities, decision making, and power [98]. Everyone on the team employs their expertise, knowledge, and skills, working collectively on a shared, patient-centered goal or outcome [98; 99].

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 [97]. At the heart of this are two other key features: mutual trust/respect and communication [99]. 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 [100]. This includes [100]:

- 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 professionals 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 [78]. 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, so students can effect positive social change [78].

CONCLUSION

In the more than three decades since the introduction of the IAT, the implicit bias knowledge base has grown significantly. It is clear that most people in the general population hold implicit biases, and health professionals are no different. While there continue to be controversies regarding the nature, dynamics, and etiology of implicit biases, it should not be ignored as a contributor to health disparities, patient dissatisfaction, and suboptimal care. Given the complex and multifaceted nature of this phenomenon, the solutions to raise individuals' awareness and reduce implicit bias are diverse and evolving.

RESOURCES

American Bar Association
Diversity and Inclusion Center
Toolkits and Projects
https://www.americanbar.org/groups/diversity/resources/toolkits

National Implicit Bias Network
https://implicitbias.net/resources/resources-by-category

The Ohio State University
The Women's Place: Implicit Bias Resources
https://womensplace.osu.edu/resources/implicit-bias-resources

The Ohio State University
Kirwan Institute for the Study of Race and Ethnicity
http://kirwaninstitute.osu.edu

University of California, Los Angeles
Equity, Diversity, and Inclusion: Implicit Bias
https://equity.ucla.edu/know/implicit-bias

University of California, San Francisco,
Office of Diversity and Outreach
Unconscious Bias Resources
https://diversity.ucsf.edu/resources/unconscious-bias-resources

Unconscious Bias Project
https://unconsciousbiasproject.org

MINDFULNESS RESOURCES

University of California, San Diego
Center for Mindfulness
https://cih.ucsd.edu/mindfulness

University of California, Los Angeles
Guided Meditations
https://www.uclahealth.org/programs/marc/free-guided-meditations/guided-meditations

Mindful: Mindfulness for Healthcare Professionals
https://www.mindful.org/mindfulhome-mindfulness-for-healthcare-workers-during-covid

FACULTY BIOGRAPHY

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.

Previously acting as a faculty member at Capella University and Northcentral University, Dr. Yick Flanagan is currently a contributing faculty member at Walden University, School of Social Work, and a dissertation chair at Grand Canyon University, College of Doctoral Studies, working with Industrial Organizational Psychology doctoral students. She also serves as a consultant/subject matter expert for the New York City Board of Education and publishing companies for online curriculum development, developing practice MCAT questions in the area of psychology and sociology. Her research focus is on the area of culture and mental health in ethnic minority communities.

Customer Information/Evaluation insert located between pages 40–41.

Pharmacologic and Medical Advances in Obesity Management

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

Course Objective
The purpose of this course is to ensure that providers have current and accurate knowledge regarding the available pharmacologic and surgical options to improve outcomes among their patients, with the ultimate goal of improving patient care and outcomes.

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

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

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

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

Division Planner
Mary Franks, MSN, APRN, FNP-C

Senior Director of Development and Academic Affairs
Sarah Campbell

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

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

Designations of Credit

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

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

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

AACN Synergy CERP Category A.

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About the Sponsor

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

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

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

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

INTRODUCTION

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

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

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

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

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

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

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

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

DEFINITIONS OF OBESITY

Which waist circumference parameters define central adiposity?

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

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

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

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

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

- Outward signs or symptoms: In patients with obesity, an increase in adiposity, commonly assessed via BMI, is the primary outward sign or symptom.
- Causes morbidity or mortality: Obesity is associated with multiple complications that confer morbidity and mortality.

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*

- Involves impaired function of ≥1 tissue: Two examples of abnormal tissue function are readily identified:
  - With expansion, adipose tissue becomes inflamed and the secretion of adipocytokines is dysregulated, resulting in alterations in metabolism and vasculature and the progression of cardiometabolic disease.
  - Interactions involving satiety hormones and central nervous system (CNS) feeding centers are abnormal, resulting in increased caloric intake and body mass.

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

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

CLINICAL ASSESSMENT

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

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

Although BMI is important, there is a growing body of evidence demonstrating the impact of central adiposity on obesity-related metabolic diseases, including diabetes [32]. A study was published that compared BMI, waist circumference, and waist-to-hip ratio in predicting the development of type 2 diabetes [33]. Researchers used information collected in the Health Professionals Follow-Up Study, a prospective cohort study of 27,270 men who were followed for 13 years. During the follow-up period, 884 men developed type 2 diabetes. Waist circumference was the best predictor. Men with waists greater than 34 inches were twice as likely to develop diabetes compared to men with smaller waist sizes (i.e., <34 inches); men with waist sizes greater than or equal to 40 inches were more than 12 times more likely to develop diabetes than men with smaller waist sizes [33]. In another study, researchers looked at waist circumference, waist-to-hip ratio, and central and subcutaneous adipose tissue measured by computed tomography (CT) as predictors of diabetes in people participating in the Diabetes Prevention Program [34]. They found that waist-to-hip ratio and waist circumference predicted diabetes; CT measurement of central adiposity also predicted diabetes but was not found to offer an important advantage over the simpler measurements. Subcutaneous adipose tissue, on the other hand, did not predict diabetes.

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

The AMA policy recognizes that [35]:

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

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

EPIDEMIOLOGY

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

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

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

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

POPULATION PREVALENCE

Adults 20 Years of Age and Older

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

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

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

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

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

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 6.0% 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.

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*

INCIDENCE

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

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

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

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

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

PERSONAL AND SOCIETAL BURDEN OF OBESITY

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

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

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*

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 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*

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

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

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

ETIOLOGY OF THE OBESITY EPIDEMIC

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

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

DIET, PHYSICAL ACTIVITY, AND BMI

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

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

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

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

Macronutrient Intake and BMI: 1965–2011

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

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

Dietary Changes: 1999–2016

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

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

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

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

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

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

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

Weight Loss Attempts: 1999–2016

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

Repeated weight loss efforts may also contribute to weight gain, which experts have suggested has created a "weight-loss futility cycle" that characterizes the rising prevalence of both obesity and weight loss attempts since 1980. The increasing prevalence of obesity and weight loss attempts has also been

paralleled by an increase in body weight stigma, which in turn is associated with many adverse health outcomes, including higher risk of all-cause mortality, and disproportionately affects individuals with obesity [65].

ENERGY EXPENDITURE RESEARCH

What is basal energy expenditure?

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

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

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

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

Additive versus Constrained Models of Metabolic Physiology

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

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

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

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

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

Energy Compensation

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

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

Resting Energy Expenditure in Healthy Underweight Adults

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

Declining Metabolic Rate and Rising Obesity

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

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

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

OTHER POTENTIAL ETIOLOGICAL FACTORS

Urbanization

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

Social Contagion

What is the role of social contagion on obesity rates?

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

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

Medication-Induced Weight Gain

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

Dietary Sugar and Sugar-Sweetened Beverages

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

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

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

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

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

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

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

SUMMARY

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

That the obesity epidemic lacks a clear explanation is a striking and poorly appreciated fact. The widely accepted causes of ever-increasing caloric intake and progressively declining physical activity are largely unsupported [16; 17]. Genetic, developmental, and environmental factors are thought to interact to cause cumulative positive energy balances resulting in weight gain and obesity [92]. Numerous factors have been associated with increased risk of obesity—but a risk factor is not necessarily a cause, and risk factors are not direct causes of disease. Associations in the obesity literature often reflect information bias, reverse causality, erroneous causal inferences, or confounding from other social and behavioral factors [54]. Although spurious, some persist to mislead science, practice, and the public [59].

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

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

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

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

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

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

THE REGULATION OF BODY WEIGHT

ENERGY BALANCE

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

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

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

Energy Intake and Storage

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

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

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

Three States of Energy Balance

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

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

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

DEFENSE OF BODY WEIGHT

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

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

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

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

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

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

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

OVERVIEW OF CLINICAL MANAGEMENT

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

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

What are the four pillars of obesity care?

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

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

Healthful Nutrition

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

Physical Activity

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

Behavior Modification

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

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

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

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

Medical Management

Antiobesity Medications

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

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

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

Bariatric Procedures

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

OBESOGENIC MEDICATIONS

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

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

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

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

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

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*

PRIORITIZATION FOR PATIENTS WITH OBESITY AND CARDIOMETABOLIC DISEASE

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

TREATING TO TARGET WITH ANTIOBESITY MEDICATIONS

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

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

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

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

Similarly, percent total weight loss is a more appropriate biomarker than body weight or BMI. Second-generation antiobesity medications allow clinicians to reach targets of weight loss that will predictably treat or prevent a broad spectrum of complications in ABCD [3]. Weight reductions of ≥10%, ≥15%, or 20% or more may be required for improvement in

certain weight-related complications and are often more desired therapeutic goals in clinical practice [133]. Depending on the complication profile, the target for percent total weight loss can be individualized [3].

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

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

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

ANTIOBESITY MEDICATIONS

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

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

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

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

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

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

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

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

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

INDICATIONS FOR USE

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

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

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

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

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

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

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

Strength of Recommendation: Weak for

FDA-APPROVED AGENTS

For Monogenic Obesity Syndromes

Setmelanotide (Imcivree)

For whom is setmelanotide contraindicated?

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

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

Bremelanotide

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

Metreleptin

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

For Short-Term Use: Sympathomimetic Amines

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

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

Phentermine (Adipex-P, Lomaira)

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

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

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

Diethylpropion (Tenuate)

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

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

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

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

Other Medications

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

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

For Long-Term Use

Gelesis100 Oral Hydrogel (Plenity)

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

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

Orlistat (Xenical, Alli)

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

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

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

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

Phentermine/Topiramate ER (Qsymia)

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

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

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

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

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

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

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

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

Naltrexone/Bupropion ER (Contrave)

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

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

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

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

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

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

Cagrilintide

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

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

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

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

CagriSema combines cagrilintide with semaglutide to produce an additive effect on appetite reduction and weight loss [163]. In a trial of adults with obesity, mean weight loss at 20 weeks was 17.1% with CagriSema, compared with 9.8% with semaglutide 2.4 mg [147]. Among 92 adults with type 2 diabetes and BMI ≥27 randomized to once-weekly CagriSema, semaglutide,

or cagrilintide (all escalated to 2.4 mg), mean weight loss at week 32 with CagriSema (15.6%) was significantly greater than semaglutide (5.1%) or cagrilintide (8.1%). Mild or moderate gastrointestinal adverse effects were common and comparable. No moderate or greater hypoglycemia was reported [164].

Retatrutide (LY3437943)

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

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

Survodutide (BI 456906)

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

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

AMG-133

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

Bimagrumab (BYM338)

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

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

Orforglipron (LY3502970)

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

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

Danuglipron

Danuglipron is another oral GLP-1 RA under development for type 2 diabetes and obesity and is taken twice-daily with food [147]. A phase 2b trial randomized 411 adults with type 2 diabetes to placebo or danuglipron. At week 16, mean weight loss difference vs placebo was –2.04 kg and –4.17 kg with danuglipron 80 mg and 120 mg, respectively. The most common adverse effects were nausea, diarrhea, and vomiting.

Only 77% of patients completed the trial [172]. In a 12-week, dose-escalation study of adults with type 2 diabetes, discontinuation from danuglipron due to adverse effects ranged from 27.3% to 72.7% [173]. In December 2023, Pfizer halted its trial of twice-daily danuglipron in response to high drop-out rates related to unacceptable side effects; the once-daily trial continued [309].

Ecnoglutide

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

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

Mazdutide

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

APH-012

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

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

ARD-101

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

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

HU6

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

Nabilone

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

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

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

NNC9204-1177

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

CLINICAL USE OF ANTIOBESITY MEDICATIONS

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

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

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

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

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

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

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

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

Practical Tips for Success with GLP-1 Agonists

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

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

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].

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*

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

Off-Label Prescribing of Antiobesity Medications

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

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

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

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

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

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

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

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

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

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

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

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

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

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

BARIATRIC SURGICAL PROCEDURES AND DEVICES

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

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

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].

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*

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

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

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

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

Roux-en-Y Gastric Bypass (RYGB)

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

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

Efficacy

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

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

Sleeve Gastrectomy

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

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

Efficacy

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

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

Laparoscopic Adjustable Gastric Banding (LAGB)

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

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

Efficacy

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

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

Biliopancreatic Diversion with Duodenal Switch (BPD/DS)

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

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

Efficacy

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

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

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

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

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

Efficacy

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

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

One-Anastomosis Gastric Bypass (OAGB)

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

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

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

Efficacy

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

ENDOSCOPIC BARIATRIC TECHNIQUES

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

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

Endoscopic Sleeve Gastroplasty (ESG)

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

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

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

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

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

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

Laparoscopic Gastric Plication

Laparoscopic gastric plication is also referred to as a primary obesity surgery endoluminal (POSE) procedure. This incisionless procedure creates full-thickness plications in the gastric fundus and body using anchors that effectively reduce gastric capacity. Whereas endoscopic suturing is somewhat reversible, laparoscopic gastric plication places polypropylene anchors with baskets cinched on either end of tissue folds and is designed for permanent gastric remodeling. To accomplish this,

it uses the incisionless operating platform, a medical device. As with ESG, laparoscopic gastric plication is associated with fewer adverse events compared with other bariatric procedures. The most common complaints are abdominal pain, nausea, and vomiting [127; 135; 239].

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

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

Intragastric Balloon Devices

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

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

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

Orbera Balloon Device

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

Obalon Balloon System

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

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

ReShape Duo Balloon

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

AspireAssist

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

OTHER OPTIONS

The TransPyloric Shuttle (TPS)

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

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

Vagal Nerve Blocking Therapy (Vbloc)

With vagal nerve blocking therapy, a pacemaker-like implantable device is surgically placed under the skin, with lead wires placed laparoscopically around the vagus nerve just above the stomach. Activation of the device causes intermittent vagal blockade to induce a sense of satiety. It is FDA approved for

weight management in patients with BMI >40 or BMI >35 with weight-related complications [127; 135]. Contraindications include cirrhosis, portal hypertension, hiatal hernia, and other implanted devices (e.g., pacemakers, defibrillators) [127; 135].

In one study, weight loss ≥10% and ≥15% at 12 months (39% and 22%) and 24 months (34% and 21%) was similar among all 123 patients. Adverse events included nausea, reflux, and pain at regulator site. No new adverse effects were noted in the second year of the two-year trial [248]. Weight loss is superior to sham-treated controls but lower than conventional MBS. Despite good safety, the modest efficacy may limit the desirability of intermittent vagal blockade [4].

Liposuction

While not a bariatric procedure, liposuction is a common esthetic procedure that can remove significant amounts of subcutaneous adipose tissue without affecting visceral adipose tissue. In a small 12-week study, women with and without diabetes had 9.1–10.5 kg body fat loss and reduced waist circumference but no improvement in blood pressure, inflammatory markers, or insulin sensitivity [4]. Removal of subcutaneous adipose tissue without reducing ectopic fat depots has little influence on the risk factors related to overweight or obesity [4].

IMPACT ON OBESITY-RELATED CARDIOMETABOLIC ENDPOINTS

MBS effects on major adverse cardiovascular events (a composite of coronary artery events, cerebrovascular events, heart failure, or cardiovascular death), major adverse liver outcomes (progression to cirrhosis, development of hepatocellular carcinoma, liver transplantation, or liver-related death), and obesity-related cancer is of considerable interest [249]. Addressing this are meta-analyses and matched-cohort studies comparing the long-term outcomes of MBS to usual obesity care (controls). Most of these data are retrospective. A noteworthy exception generating many studies is the Swedish Obese Subjects (SOS) project, which has prospectively followed 4,000 bariatric and control patients and a random population reference group of 1,135 over more than 20 years with >98% patient follow-up [250].

In cardiovascular disease outcomes, MBS has been associated with a significantly reduced risk of cardiovascular mortality and incidence of heart failure, myocardial infarction, and stroke [129]. In a 2020 SOS study, patients who had undergone MBS were 30% less likely to die from any cardiovascular disease than controls, including myocardial infarction, heart failure, and stroke, and were 23% less likely to die from cancer. Median life expectancy of MBS patients was 3.0 years longer than controls but 5.5 years shorter than the general population [250].

A 2021 systematic review and meta-analysis found increased median life expectancy of bariatric patients of 9.3 years in those with pretreatment diabetes and 5.1 years among those with no pretreatment diabetes compared with controls. The authors responded to the shorter life expectancy gain from MBS in the 2020 SOS study by citing residual confounding and outdated procedures [251].

In a 2023 SOS study, MBS increased life expectancy by 2.1 and 1.6 years in patients with and without diabetes at a median 26-year follow-up. These authors criticized the 2021 systematic review and meta-analysis for reliance on relatively short-term retrospective data and control patients captured from registers with limited information on health status. MBS benefit in pretreatment type 2 diabetes partly depends on irreversible organ damage (more common with long diabetes duration) and whether short-term or durable remission is achieved (also affected by the severity and duration of diabetes) [252].

Among obese adults with NASH and liver fibrosis, 10-year cumulative incidence of major adverse liver outcomes was 2.3% in those who underwent MBS, compared with 9.6% in controls; major adverse cardiovascular events occurred in 8.5% of MBS participants, compared with 15.7% among controls. For patients with NASH and obesity, MBS was associated with a significantly lower risk of incident major adverse liver outcomes and major adverse cardiovascular events than nonsurgical management [249].

Ten-year outcomes significantly favored MBS in obesity-related cancer incidence (2.9% vs 4.9%) and mortality (0.8% vs 1.4%). Comparable RYGB and sleeve gastrectomy outcomes suggest the primary mechanism is weight loss itself, not procedure-specific physiological alteration. Among MBS patients, cancer incidence was highest in those with weight loss less than 24%. Dose-dependent reduction in cancer risk required substantial weight loss, and the separation of survival curves only appeared six years after the index date [130].

POSTBARIATRIC INTERVENTIONS

Greater comprehension of obesity as a chronic disease requiring long-term management has highlighted the importance of intervention in patients with primary or secondary MBS nonresponse [214]. Nonresponse has been defined as <50% excess weight loss over one to two years following intervention, and weight recurrence is defined as regaining ≥20% of nadir weight loss after MBS [224; 253]. Weight recurrence refers to secondary nonresponse [214]. Estimated rates of nonresponse (11% to 22%) and weight recurrence (16% to 37%) vary by definition used [224; 254].

Causes of weight recurrence include increased caloric intake due to increased appetite and maladaptive or dysregulated eating, inadequate physical activity, and psychosocial stresses. Weight recurrence can promote recurrence of previously controlled type 2 diabetes and other obesity-related complications, with diminished quality of life and poor emotional health. Preventing weight recurrence is a primary goal [224].

Surprisingly, nutritional, cognitive-behavioral, supportive, and other psychological and lifestyle interventions, started perioperatively or up to two years postoperatively, have not demonstrated a significant effect on overall weight loss. Sys-

tematic 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].

Peripheral Signals of Energy Status

What effect does ghrelin have on energy balance and obesity?

As will be discussed later in this course, many novel and emerging antiobesity medications act through the hypothalamic receptors of peripherally released hormones and peptides. ***Table 10*** summarizes the effects of endogenous and pharmacological ligand-binding of these receptors.

Adipose Tissue and Pancreatic Hormones

Some peripheral signals of energy balance are released by adipocytes (leptin, adiponectin), and pancreatic α cells (GCG), β cells (insulin, amylin), and F cells (pancreatic polypeptide) [150; 282].

Leptin, the canonical signal of adipose tissue mass, is produced by white adipose tissue in approximate proportion to triglyceride stores. Adequate leptin action via its receptor (LepR) on arcuate neurons indicates sufficient energy stores; reduced leptin signaling indicates an energy deficit, promoting hunger and increasing energy intake [281]. LepR activation also decreases body weight by increasing lipolysis and energy expenditure [277]. CCK potentiates leptin effects to decrease food intake and body weight [267].

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*

Normal body-weight maintenance requires intact leptin-regulated neurocircuits. An association of obesity with leptin resistance has been suggested, but some obese individuals may simply require more leptin to fully engage relevant neurocircuits. The primary role of leptin-responsive neurocircuits may relate more to preventing loss of body fat (by decreased leptin signaling to CNS) than defending against its increase (by increased leptin levels) [7].

Adiponectin is an adipocyte-derived protein that decreases body weight and plasma lipid levels and enhances insulin suppression of hepatic glucose production. Adiponectin levels increase following weight loss interventions in obesity, and patients with obesity show an inverse correlation between plasma adiponectin and insulin resistance [115].

Insulin and leptin both circulate in proportion to fat mass. Insulin activates its receptor (IR) expressed in the melanocortin system, which mediates its central anorexigenic effects, decreasing food intake and body weight [115]. Insulin also acts centrally to decrease hepatic glucose output, in part by inhibiting hypothalamic neurons [102]. Insulin inhibits AgRP neuron firing via IR-dependent signaling. Disruption of IR in the CNS promotes obesity with increases in body fat and leptin levels, insulin resistance, elevated insulin levels, and hypertriglyceridemia [266].

Amylin is co-released with insulin from pancreatic β-cells in response to high blood glucose levels, reduces the rate of glucose absorption and inhibits glucagon release. Amylin receptor complexes in the area postrema and brainstem NTS mediate its anorectic effects by activating a central satiety pathway. Amylin also affects hedonic eating by inhibiting reward neurocircuits [141; 267]. Amylin and leptin act synergistically, in part by amylin acting directly on AgRP neurons that co-express LepR. Amylin's ability to slow post-prandial gastric emptying also contributes to satiety [141].

Glucagon (GCG) is secreted by pancreatic α-cells and binds its receptor (GCGR) in the CNS, pancreas, adipocytes, and liver. Glucagon stimulates energy expenditure, reduces food intake, and decreases body weight through multiple mechanisms, including inducing satiety and lipolysis [147; 267]. Hypothalamic GCGR activity inhibits AgRP neuron activity to attenuate orexigenic effects, while central resistance to glucagon-induced hypophagia contributes to the development of obesity [141]. Glucagon's anorectic action seem to be mediated via the liver-vagus-hypothalamus axis [267].

Gut Peptide Hormones

Other signals of energy balance are released by enteroendocrine cells that line the gut, one of the largest hormone-producing organs. Enteroendocrine cells and their respective hormones include L-cells (GLP-1, OXM, PYY), I-cells (CCK), K-cells (GIP), and P/D1 cells (ghrelin). Gut hormones bind their receptors in CNS and on pancreatic β cells (GLP-1, GIP), pancreas (CCK, OXM), and adipocytes (GIP) [147; 267; 283].

Meal termination involves meal-induced enteroendocrine cells release of peptides (e.g., GLP-1, CCK), which promote satiety by activating vagal afferent neurons that relay GI signals to brainstem areas, including the NST [7]. Glucagon-like peptide 1 (GLP-1) increases in circulation following meals and decreases during fasting, stimulates insulin secretion and regulates energy intake, and is also produced in the NTS. GLP-1 acts on GLP-1R in the gut and brain to delay gastric emptying and decrease food intake through activation of satiety pathways and efferent pathways regulating GI function. GLP-1 also reduces glucagon secretion, inhibiting hepatic glucose production [284].

GLP-1 inhibits eating mainly by activating GLP-1R on hypothalamic and brainstem NTS neurons. GLP-1R agonists also suppress hedonic eating by interacting with the mesolimbic reward system, including the ventral tegmental area and nucleus accumbens [267]. GIP and GLP-1 are rapidly degraded by the enzyme dipeptidyl peptidase IV (DPP-IV), leading to a circulating half-life of only two minutes for GLP-1 [150].

GIP acts in concert with GLP-1 on the pancreas after meals to regulate blood glucose by stimulating insulin and glucagon release. GIP contributes to lipid metabolism by promoting lipid storage, adipose tissue blood flow, and triglyceride uptake in adipocytes [284]. The GIP receptor (GIPR) is expressed in arcuate, dorsomedial hypothalamus, and PVH neurons; GIPR activation reduces food intake [267].

Ghrelin circulates as an orexigenic signaler, promoting hunger and meal initiation by binding its receptor (GHSR) on AgRP neurons, which stimulates NPY and AgRP release and inhibits POMC neurons by increasing GABAergic signaling. Vagal afferent neurons also have ghrelin receptors [115; 267]. Compared with lean controls, individuals with obesity have lower circulating ghrelin levels and are more sensitive to its appetite-stimulating effects [115; 267].

Ghrelin and leptin have a reciprocal relationship aimed at increasing or decreasing adiposity. Fasting increases ghrelin and reduces leptin, while high leptin levels suppress gastric ghrelin release and prevent ghrelin-induced NPY neuron activation [141]. Ghrelin and GLP-1 have opposite actions on eating behaviors. Ghrelin reinforces food reward by activating ventral tegmental area dopaminergic neurons; GLP-1 attenuates various palatable food-motivated efforts [267].

Ghrelin remains the only metabolic signal that potently activates orexigenic AgRP neurons. Discovery of an endogenous antagonist of ghrelin, liver-expressed antimicrobial peptide, sparked research interest in it as a possible candidate for obesity treatment [267].

CCK is secreted postprandially and binds CCK1 receptors (CCK1R) expressed in the vagal afferents, brainstem, and hypothalamus to decrease food intake. The satiety signals of CCK are transmitted to the NTS by vagal sensory neurons. CCK activates NTS POMC neurons, and brainstem MC4R signaling is required for CCK-induced appetite suppression [267]. CCK is an acutely acting signal with a very short half-life. Compensatory increases in meal frequency prevent CCK from producing long-term effects on total food intake or body weight [102].

OXM is secreted with GLP-1 and PYY in the postprandial state and exerts its anorectic action primarily via GLP-1R and secondarily via GCGR. The GLP-1R-mediated effects of OXM differ from those of GLP-1. OXM decreases body weight by lowering food intake and increasing energy expenditure and may act via different hypothalamic pathways than those of GLP-1 [267].

PYY is co-secreted with GLP-1 following a meal. Its major circulating form (PYY3-36) binds Y2R expressed on AgRP neurons, inhibiting these neurons and activating POMC neurons. Thus, PYY reduces appetite and body weight by increasing anorexigenic melanocortic activity in the arcuate [267].

PATHOPHYSIOLOGY

Long-term positive energy balance and increased fat mass promote pathogenic adipocyte hypertrophy and adipose tissue accumulation and dysfunction, resulting in immunopathies, endocrinopathies, increased circulating free fatty acids, and lipotoxicity. The OMA uses the term adiposopathy, or "sick fat disease," to describe pathogenic adipose tissue [128].

The consequences of adiposopathy contribute to metabolic diseases including type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, NAFLD, and cancer [18; 29]. Obesity-related metabolic and cardiovascular diseases can be termed cardiometabolic disease or metabolic syndrome.

Adiposopathy is analogous to the disease state of other organs, such as myopathy, cardiomyopathy and encephalopathy. In the disease of adiposopathy, pathogenic enlargement of fat cells and the fat organ results in anatomic and functional abnormalities, metabolic and biomechanical morbidities, and increased mortality [18; 29].

Adipose Cell and Tissue Function

Part of understanding obesity as a disease is recognizing that adipocytes and adipose tissue have vital functions beyond energy storage alone [128]. Adipose tissue is mostly comprised of adipocytes, regulates multiple body processes critical to energy and metabolic homeostasis, and is functionally classified into two types: white and brown [128; 285]. White adipose tissue is an active endocrine and immune organ that includes subcutaneous adipose tissue and visceral (abdominal) adipose tissue and primarily stores energy. However, subcutaneous adipose tissue contains brown-like inducible adipocytes that perform mitochondrial and thermogenic functions and burn fat [286].

Brown adipose tissue, comprising 1% to 2% of body fat, has more mitochondria (thus its brown appearance) and is abundant in neonates but decreases in adults and decreases further in obese adults [286]. Brown adipose tissue produces heat energy, termed thermogenesis, upon β-adrenergic stimulation [287].

Subcutaneous adipose tissue is the largest fat depot. Visceral adipose tissue is more metabolically active, vascular, and innervated than subcutaneous tissue. Ectopic fat, a third depot, is strictly pathogenic [48].

Fat depots are sexually dimorphic; on average, men have more visceral adipose tissue, and women have larger subcutaneous adipose tissue stores. Given the relative impact of fat depots on metabolic health, this sexual dimorphism may explain sex differences in metabolic disease risk until menopause, when decreased estrogen may increase low-density lipoprotein, triglycerides, visceral fat, morbidity, and mortality in women [48].

Adipocytes, which constitute the largest cell volumes in adipose tissue and are the defining fat cell type, have three important roles: lipid storage, insulin sensitivity, and secretory function. Disruption of any contributes to obesity-related metabolic disease states [288].

Some key players in adipose tissue physiology and obesity pathophysiology include glucose, glycogen, triglycerides, and insulin [289; 290]. Glucose is a carbohydrate, one of three macromolecule classes (with fats and proteins); some argue alcohol is a fourth class. Glycogen is the storage form of glucose in liver and muscle. Triglyceride, the storage form of fatty acids, is made of three fatty acids linked to glycerol. The capacity to store carbohydrates (as glycogen) is limited. What cannot be stored as glycogen, or quickly used, gets stored as triglyceride. Insulin, released by pancreatic β-cells in response to rising blood glucose, aims to store carbohydrate as glycogen or fatty acids.

Lipid Storage

During energy surplus, 60% to 80% of excess calories are stored as triglyceride by adipocytes [291]. Adipocytes can increase fat stores (lipogenesis) or release fatty acids (lipolysis) to supply other tissues with energy [278; 285]. Insulin is critically involved in these processes.

For lipogenesis, adipocytes accumulate lipid through free fatty acids from circulating triglyceride and by synthesizing triglyceride from non-lipid metabolite sources, termed de novo lipogenesis [285]. For lipolysis, enzymatic cleavage of triglyceride by lipases generates glycerol and free fatty acids, which are released into circulation for use by organs as fuel (e.g., glycerol for liver gluconeogenesis) [288]. Lipolysis is controlled by sympathetic nervous system input and norepinephrine. In the fasting state, insulin levels drop, releasing norepinephrine, which promotes lipolysis [288].

Because adipose tissue is central to the regulation of systemic lipid metabolism, a balance between lipogenesis and lipolysis within adipocytes is required to maintain insulin sensitivity and energy homeostasis. Nutrient (free fatty acids and glucose) and hormonal cues regulate both processes [288].

Insulin Sensitivity

Insulin sensitivity of adipose tissue is vital to metabolic homeostasis and systemic energy balance [285]. Insulin binds to its receptor in liver, muscle, and adipose tissue to initiate several processes [48; 292].

Insulin activates glucose transporter-4 (GLUT4) on cell surfaces, which transport glucose from the bloodstream into cells. On fat cells, insulin accelerates glucose delivery into adipocytes and induces breakdown of glucose into triglycerides for storage.

Insulin upregulates lipoprotein lipase on fat cell surfaces that bring free fatty acids into adipocytes to store them triglycerides. Insulin also increases triglyceride accumulation by inhibiting their breakdown and release as free fatty acids.

The primary source of glucose for all tissues and largest glucose storage site (as glycogen) is the liver. Hepatocytes are critical intermediaries in energy (lipid, carbohydrate) metabolism. Insulin decreases glucose output by the liver, the main target for pancreatic insulin and glucagon [292; 293].

During caloric deficit, low insulin disinhibits lipolysis, which mobilizes lipids to meet energy demand. However, elevated insulin during caloric excess stimulates glucose uptake, inhibits lipolysis, and orchestrates de novo lipogenesis. The body goes into "storage" mode of carbohydrates and fat. These normal functions of insulin help protect against the cellular and tissue toxicity caused by high circulating glucose and free fatty acids [285; 289].

Endocrine and Immune (Secretory) Function

As an endocrine/immune organ, adipose tissue releases adipokines (via adipocytes) and receives (via receptors) metabolic signals to influence and regulate adipogenesis, lipid metabolism (lipogenesis and lipolysis), appetite and energy balance, inflammatory and immune response, glucose homeostasis (insulin sensitivity), vascular homeostasis (endothelial function), blood pressure, and other processes [128; 285; 288].

Adipokines are hormones, cytokines, extracellular matrix proteins, and growth factors that transmit information from fat tissue to other metabolic organs. They can act locally (paracrine) and/or systemically (endocrine) [128; 285]. Adipocytes express receptors for nuclear and traditional hormones, adipokines, neuropeptides, lipoproteins, prostaglandins, endocannabinoids, and others [128]. Several adipokine hormones, including leptin and adiponectin, are regulators of systemic lipid and glucose homeostasis [285; 288; 294].

Accordingly, adipose tissue can release pro-inflammatory hormones (leptin), cytokines (e.g., tumor necrosis factor-alpha [TNF-a], interleukin-6 [IL-6], IL-8), acute phase response proteins (e.g., C-reactive protein [CRP]), chemokines (e.g., monocyte chemoattractant protein–1 [MCP-1]), and prostaglandins. In addition, adipose tissue can release anti-inflammatory hormones (adiponectin), interleukins (IL-10), and transforming growth factor beta 1 (TGF-beta) [128; 295; 296].

Pathogenesis of Adiposopathy and Obesity-Related Complications

An immune response appears early during adipose accumulation. With excessive fat mass, local adipose-induced inflammatory processes progress to widespread systemic inflammation that damages distant tissue and induces a host of metabolic disorders and organ tissue complications in obesity [194; 297].

Local Pathogenesis

Adipose tissue contains adipocytes, vascular cells, fibroblasts, cells of the innate (e.g., monocytes, macrophages, natural killer cells) and adaptive (e.g., lymphocytes) immune systems, and other cell types essential to its normal physiology that become abnormally altered and interact in the pathophysiology of obesity-related cardiometabolic complications [285; 296]. To expand triglyceride storage as obesity develops and fat mass increases further, adipocytes abnormally increase in number (hyperplasia), then in size (hypertrophy) [278; 285]. Hypertrophy compromises the function of adipose tissue, degrading the extracellular matrix which promotes a switch toward fibrosis that restricts adipocyte fat storage [295; 298].

Triglyceride accumulation promotes hypoxia, apoptosis, and oxidative and mitochondrial stress in adipocytes and release of pro-inflammatory factors [287; 296]. As obesity advances, lipid-laden hypertrophied adipocytes undergo necrotic and/or apoptotic cell death, contributing to the recruitment of inflammatory cells and to adipose tissue dysfunction [298].

Adipose tissue macrophages are essential for maintaining adipose tissue energy homeostasis and inflammatory response [291]. The adipose tissue macrophage phenotypic correlates to BMI and adipocyte size [296]. The obesity-induced M1 phenotype is associated with inflammation and tissue destruction; M1 may comprise 50% of all adipose tissue cells (compared with 10% to 15% in lean adults) [298; 299].

As adipose tissue expands, angiogenesis lags. The hypoxic state triggers an inflammatory response, which initiates monocyte recruitment and differentiation into M1 adipose tissue macrophages [299]. Circulating macrophages infiltrate adipose tissue, producing MCP-1, which recruits more inflammatory cells to adipose tissue and TNF-a and further promotes MCP-1 production by adipocytes, recruiting yet more immune cells to adipose tissue. The M2 to M1 shift aggravates a vicious cycle of chronic low-grade inflammation [128; 285].

Systemic Pathogenesis

The inflammatory adipose tissue microenvironment diffuses systemically and to remote organ sites. MCP-1 recruitment and proliferation into liver, adipose, pancreatic islet, intestine, and muscle tissue induces a pro-inflammatory M1 state [299]. Cytokines (TNF-a, IL-1b, IL-6) and adipokines (leptin) activate systemic and organ-specific inflammatory signaling pathways, impairing β-cell function, suppressing insulin secretion, and promoting accumulation of ectopic fat, insulin resistance and hyperglycemia [287; 297; 298; 300].

Adiposopathic tissue pumps free fatty acids into circulation, leading to ectopic pathogenic deposition of fatty acids into pericardial and perivascular fat depots, within/around the liver, muscle, heart, pancreas, and kidney [128]. Ectopic fat intensifies local inflammatory activity and promotes lipotoxicity [300].

Insulin resistance in adipocytes impedes fat storage, accelerates lipolysis and further increases plasma free fatty acids, promoting insulin resistance in liver and muscle, hepatic steatosis and dyslipidemia, and contributing to β-cell failure. Insulin resistance in muscle and fat is marked by impaired glucose transport from circulation due to M1 inhibition of GLUT4, leading to hyperglycemia [301].

Increased ectopic fat deposition, lipotoxicity from excess circulating free fatty acids, glucose toxicity, along with β-cell resistance to GLP-1, cause progressive failure of β-cell functioning. Increased glucagon and enhanced liver sensitivity to glucagon lead to excessive hepatic glucose production. Increased renal glucose reabsorption by sodium/glucose co-transporter 2 (SGLT2) helps maintain hyperglycemia.

Insulin resistance in obesity leads to chronic compensatory hyperinsulinemia, which in turn promotes further weight gain [302]. This is exacerbated by resistance to the anorexigenic effects of insulin, leptin, GLP-1, amylin, and PYY [303].

Insulin resistance, hyperglycemia, and hyperinsulinemia in obesity promote hypertension, dyslipidemia, endothelial dysfunction, and a prothrombotic state, leading to NAFLD and type 2 diabetes [304]. NAFLD increases the risk of liver cirrhosis and hepatocellular carcinoma and is strongly correlated with cardiovascular disease and type 2 diabetes [305].

Type 2 diabetes, the predominant consequence of insulin resistance accounting for more than 90% of all diabetes cases, can lead to disabling and life-threatening microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (cardiovascular disease) complications [304; 306].

Biomechanical Consequences of Obesity

Local biomechanical stress due to excessive fat mass and body weight (e.g., on the joints, respiratory tract, blood vessels or within the abdominal compartment) causes and/or exacerbates morbidities common in patients with obesity, such as knee osteoarthritis, back pain, restrictive lung disease, obstructive sleep apnea, gastroesophageal reflux disease (GERD), hernias, and chronic venous insufficiency. These complications are further aggravated by the adverse metabolic profile and chronic inflammatory state in obesity, amplifying the overall burden of the disease and creating a vicious cycle that can be effectively broken only by sustained weight loss [302].

"Metabolically Healthy" Obesity

The concept of metabolically healthy obesity has been described in the literature. In general, it is defined as obesity in the absence of type 2 diabetes, hypertension, and hypercholesterolemia. Some have questioned the cardiovascular disease risk of persons with metabolically healthy obesity, suggesting this as a low-risk phenotype [307]. However, a large cohort demonstrated that obesity is a risk factor for cardiovascular disease regardless of whether the individual remained metabolically healthy over long periods [308]. Furthermore, a study of 270 patients who met strict inclusion criteria for metabolically healthy obesity found that even with strict criteria to eliminate all patients with any metabolic problems, a significant proportion had unsuspected NAFLD (35.5%); some had steatohepatitis (8.2%) and liver fibrosis (4.4%) [305].

Psychiatric Disorders

The neuropathological processes that lead to psychiatric disorders share common brain pathways with those that lead to obesity, metabolic syndrome, and cardiovascular disease risk factors, each of which can influence the risk for the others. Evidence points to a critical role for two major pathways: inflammatory processes that induce alterations of brain functions, and chronic stimulation of the hypothalamic-pituitary-adrenal (HPA) axis [87].

Psychiatric disorders are often characterized by a chronic HPA axis activation and sustained cortisol elevation, both of which are linked to abdominal obesity, hepatic steatosis, insulin resistance, and cardiovascular disease. Conversely, increased adiposity leads to chronic low-grade activation of inflammatory processes, which plays a potent role in the pathophysiological brain alterations associated with psychiatric disease. Thus, adiposity-driven inflammation may contribute to the growing prevalence of mood disorders [87].

Customer Information/Evaluation insert located between pages 40–41.

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POSTOPERATIVE COMPLICATIONS

UPDATE

#30764 • 15 ANCC / 1 Pharm Hour

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to provide nurses and all allied health professionals who care for postsurgical patients the knowledge necessary to recognize and manage common postoperative complications, improving patient care and outcomes.
Faculty: Susan Engman Lazear, RN, MN
Audience: This course is designed for all nurses and allied professionals involved in the care of patients who undergo surgical procedures, especially those who work in the preoperative area, the operating room, or the postanesthesia unit in hospitals or free-standing surgical centers.
Additional Approval: AACN Synergy CERP Category A, CCMC

COMMUNICATION AND SOFT SKILLS IN NURSING PRACTICE

NEW!

#31350 • 3 ANCC Hours

Book By Mail – $26 • ONLINE – $18

Purpose: The purpose of this course is to provide nurses with strategies to support the soft skills needed to provide optimal patient care and enhance professionalism in health care.
Faculty: Mary Franks, MSN, APRN, FNP-C
Audience: This course is designed for nurses in all practice settings.
Additional Approval: AACN Synergy CERP Category C

CHILDHOOD OBESITY: IMPACT ON HEALTH CARE

#32014 • 5 ANCC / 1 Pharm Hour

Book By Mail – $38 • ONLINE – $30

Purpose: The impact of childhood obesity on an already stressed healthcare system is high and is estimated to rise as the diagnoses of comorbid conditions continue to occur at a younger age. The purpose of this course is to provide nurses with the information necessary to improve the care of children and adolescents who are overweight or obese.
Faculty: Diane Thompson, RN, MSN, CDE, CLNC
Audience: This course is designed for nurses in all practice settings with a desire to better understand the issues facing obese children and their families and the impact of childhood obesity on national and global health care.
Additional Approval: AACN Synergy CERP Category A, CCMC

PRESSURE INJURIES AND SKIN CARE

UPDATE

#34344 • 5 ANCC Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide nurses with the information necessary to accurately identify, treat, and manage skin breakdown (pressure ulcers), thereby improving patient outcomes and quality of life.
Faculty: Maryam Mamou, BSN, RN, CRRN, CWOCN
Audience: This course is designed for nurses in all practice settings, particularly those caring for patients at high risk for developing pressure injuries.
Additional Approval: AACN Synergy CERP Category A, CCMC

ETHICAL DECISION MAKING

UPDATE

#37074 • 15 ANCC Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to assist healthcare professionals to define the predominant ethical theories and principles used in health care, determine any legal and regulatory implications, and in collaboration with their colleagues and patients/clients, make effective decisions that determine the appropriate course of treatment, or refusal of such, for and with those for whom they care.
Faculty: Michele Nichols, RN, BSN, MA
Audience: This course is designed for all nurses and allied healthcare professionals.
Additional Approval: AACN Synergy CERP Category B, CCMC

DEVELOPING A SAFE OPIOID TREATMENT PLAN FOR MANAGING CHRONIC PAIN

IL MANDATE

#91042 • 1 ANCC / 1 Pharm Hour

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.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for physicians, pharmacists, nurses, and physician assistants involved in the care of patients prescribed opioids to treat pain.
Additional Approval: AACN Synergy CERP Category A
Special Approval: This course meets the 2025 Illinois requirement for opioid prescribing education.

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METABOLIC SYNDROME: A GROWING EPIDEMIC

UPDATE

#91544 • 5 ANCC / 1 Pharm Hour

Book By Mail – $38 • ONLINE – $30

Purpose: 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.
Faculty: John J. Whyte, MD, MPH
Audience: This course is designed for healthcare professionals working with adults or adolescent patients who exhibit risk factors for metabolic syndrome.
Additional Approval: AACN Synergy CERP Category A

SMOKING AND SECONDHAND SMOKE

#91784 • 10 ANCC / 5 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide physicians, nurses, behavioral health professionals, and other members of the interdisciplinary team with a formal educational opportunity that will address the impact of tobacco smoking and secondhand exposure in public health and disease as well as interventions to promote smoking cessation among their patients.
Faculty: Mark S. Gold, MD, DFASAM, DLFAPA
Audience: This course is designed for physicians, nurses, and other healthcare professionals who may intervene to stop patients from smoking.
Additional Approval: AACN Synergy CERP Category A, CCMC

CANCER SCREENING

#91993 • 10 ANCC Hours

Book By Mail – $68 • ONLINE – $60

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.
Faculty: Lori L. Alexander, MTPW, ELS, MWC
Audience: This course is designed for physicians, physician assistants, and nurses who may intervene to improve cancer screening rates.
Additional Approval: AACN Synergy CERP Category A

MATERNAL HEALTH DISPARITIES

NEW!

#93010 • 4 ANCC Hours

Book By Mail – $32 • ONLINE – $24

Purpose: The purpose of this course is to provide healthcare providers with the knowledge and skills necessary to improve maternal outcomes in all races, ethnicities, and marginalized groups.
Faculty: Mary Franks, MSN, APRN, FNP-C
Audience: This course is designed for all healthcare providers who may intervene to improve peripartum and postpartum health care and reduce health disparities.
Additional Approval: AACN Synergy CERP Category B

LOW BACK PAIN

UPDATE

#94102 • 15 ANCC / 10 Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to provide healthcare professionals with a greater understanding of the pathophysiology and differential diagnosis of low back pain conditions so they may effectively treat or manage low back pain, resulting in improved patient health, quality of life, and satisfaction.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the care of patients with back pain.
Additional Approval: AACN Synergy CERP Category A, CCMC

AUTOIMMUNE DISEASES

UPDATE

#94454 • 15 ANCC / 10 Pharm Hours

Book By Mail – $98 • ONLINE – $90

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.
Faculty: Lori L. Alexander, MTPW, ELS, MWC; John M. Leonard, MD
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 Approval: AACN Synergy CERP Category A, CCMC

PNEUMONIA

New Guidelines

#94673 • 10 ANCC / 5 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide physicians, nurses, and other healthcare professionals who manage the care of patients with pneumonia a foundation for effective management strategies in order to improve outcomes and foster an interprofessional collaborative practice consistent with published guidelines.
Faculty: Carol Whelan, APRN; Lori L. Alexander, MTPW, ELS, MWC
Audience: This course is designed for all physicians, physician assistants, and nurses, especially those working in the emergency department, outpatient settings, pediatrics, nursing homes, and intensive care units.
Additional Approval: AACN Synergy CERP Category A, CCMC

MANAGING DRUG INTERACTIONS WITH DIRECT ORAL ANTICOAGULANTS

NEW!

#95010 • 1 ANCC / 1 Pharm Hour

Book By Mail – $23 • ONLINE – $15

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 drug-drug interactions that occur in patients taking direct oral anticoagulants.
Faculty: Jeff Langford, PharmD
Audience: This course is designed for physicians, physician assistants, and nurses involved in the care of patients who require anticoagulation therapy.
Additional Approval: AACN Synergy CERP Category A

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

Course Availability List *(Cont'd)*

OPIOID SAFETY: BALANCING BENEFITS AND RISKS

NE MANDATE

#95500 • 5 ANCC / 5 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute opioids with an appreciation for the complexities of opioid prescribing and the dual risks of litigation due to inadequate pain control and drug diversion or misuse in order to provide the best possible patient care and to prevent a growing social problem.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for all physicians, osteopaths, physician assistants, pharmacy professionals, and nurses who may alter prescribing and/or dispensing practices to ensure safe opioid use.
Additional Approval: AACN Synergy CERP Category A, CCMC
Special Approval: This course meets the Nebraska APRN requirement for opioid prescribing education.

ANXIETY DISORDERS IN OLDER ADULTS

NEW!

#96690 • 3 ANCC / 1 Pharm Hour

Book By Mail – $26 • ONLINE – $18

Purpose: Older adults are the fastest growing demographic in the world, and anxiety disorders are the most common mental disorder in this age group. The purpose of this course is to provide clinicians with the knowledge and skills necessary in order to improve the assessment and treatment of anxiety disorders in older adults.
Faculty: Beyon Miloyan, PhD
Audience: This course is designed for the benefit of a broad range of allied health professionals, including but not limited to physicians, nurses, medical assistants, and nursing home administrators.
Additional Approval: AACN Synergy CERP Category A

PSYCHEDELIC MEDICINE AND INTERVENTIONAL PSYCHIATRY

NEW!

#96790 • 10 ANCC / 8 Pharm Hours

Book By Mail – $68 • ONLINE – $60

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.
Faculty: Mark S. Gold, MD, DFASAM, DLFAPA
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 Approval: AACN Synergy CERP Category A, CCMC

CULTURAL COMPETENCE: AN OVERVIEW

IL MANDATE

#97430 • 2 ANCC Hours

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to provide members of the interprofessional healthcare team with the knowledge, skills, and strategies necessary to provide culturally competent and responsive care to all patients.
Faculty: Alice Yick Flanagan, PhD, MSW
Audience: This course is designed for all members of the interprofessional healthcare team.
Additional Approval: AACN Synergy CERP Category B
Special Approval: This course meets the 2025 Illinois requirement for cultural competence education.

THE SCOOP ON COLLAGEN

NEW!

#98070 • 1.5 ANCC Hours

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the various collagen products.
Faculty: Chelsey McIntyre, PharmD
Audience: This course is designed for healthcare professionals whose patients are taking or are interested in taking collagen products.
Additional Approval: AACN Synergy CERP Category A

ANEMIA IN THE ELDERLY

#99084 • 5 ANCC / 2 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide healthcare providers with the knowledge and tools necessary to identify anemia early and respond appropriately. Better health outcomes for the geriatric population will result from an increase in evidence-based clinical practices.
Faculty: Susan Waterbury, MSN, FNP-BC, ACHPN
Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the care of elderly patients.
Additional Approval: AACN Synergy CERP Category A, CCMC

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	97000	Implicit Bias in Health Care / 3 Contact Hours	$18
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1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review
2. _____ Hours	2. _____ Hours	2. _____ Hours	2. _____ Hours
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11. ☒ N/A	11. ☐ Yes ☐ No	11. ☒ N/A	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

#97081 Sexual Harassment Prevention: The Illinois Requirement — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

_____

#96102 Frontotemporal Dementia — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

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