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FOR MICHIGAN NURSES
2024

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Pulmonary Embolism

Includes 1 Pharmacotherapeutic/Pharmacology Hour

Audience
This course is designed for nurses, physicians, and PAs involved in assessing, triaging, and managing patients with suspected pulmonary embolism.

Course Objective
The purpose of this course is to provide healthcare professionals with the knowledge and clinical strategies necessary to optimally triage and treatment patients with pulmonary embolism.

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

1. Define a thromboembolic event.
2. Explain pathogenesis, risk factors, and demographics of pulmonary embolism (PE).
3. Review the diagnostic workup of PE.
4. Compare the different types of PE treatments in both inpatient and outpatient settings.

Faculty
Dalia Saha, MD, is a board-certified internal medicine physician with more than 15 years of clinical experience. With experience in both academic and private healthcare settings, Dr. Saha has vast exposure to many aspects of patient care and clinical medicine. Always interested in the didactic component of health care, Dr. Saha works on the education committee for the American College of Physicians and is an instructor and teaching staff for medical students and residents in George Washington University and Johns Hopkins Medical Schools. Lauded by her colleagues for her dedication and work ethic in the field of medicine, she has been awarded the Top Doctor Award in Washington, DC.

Faculty Disclosure
Contributing faculty, Dalia Saha, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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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

How are pulmonary emboli categorized?

Pulmonary embolism (PE) is very common in both inpatient and outpatient settings [1; 2]. It should be one of the first considerations when a patient presents with acute-onset dyspnea, shortness of breath, and chest pain. Other common symptoms include cough, hemoptysis, diaphoresis, and feverishness.

A PE is an abrupt occlusion of the pulmonary artery and/or one of its branches. The occlusion may consist of blood clot/thrombus, air, fat, or malignancy/tumor originating in another part of the body, which dislodges and travels through the venous system to the right side of the heart and thence the pulmonary vasculature. In most cases, PE arises from deep vein thrombophlebitis in the lower legs or pelvis, following trauma, surgery, infection, or an acquired hypercoagulable state.

The natural history of PE is variable. PE may be single or multiple (pulmonary emboli), small and clinically silent, large or recurrent with progressive obliteration of the pulmonary vascular bed, causing cardiorespiratory failure. Symptomatic PE is commonly associated with significant morbidity and mortality risk; the challenge for clinical care providers is early recognition and prompt therapeutic intervention to relieve pulmonary artery obstruction and prevent additional pulmonary emboli, any one of which could prove fatal [1; 2]. With modern technology, which can detect small embolic events, the condition is identified much earlier, making possible effective treatment prior to complete hemodynamic collapse [1; 2; 3]. Assessment and prevention in outpatient settings have also led to improvements in mortality. Research indicates that small, subclinical pulmonary emboli probably occur with some frequency but are transient in nature and go unnoticed; however,when there is predisposition to venous stasis (e.g., inflammation, injury, heart failure, coagulopathy), single large or recurrent PE becomes a challenging clinical illness requiring prompt diagnosis and treatment.

Classification of PE typically categorizes the disease as hemodynamically stable or unstable. The most common type is hemodynamically stable, which can range from small, mildly symptomatic or asymptomatic PE (previously referred to as low-risk PE or small PE) to those who present with right ventricular dysfunction but who are hemodynamically stable (previously referred to as submassive or intermediate-risk PE) [3; 4]. While PE characterized by right ventricular dysfunction can be hemodynamically stable, more severe (unstable) disease is characterized by the presence of systemic arterial hypotension, which indicates at least half of the pulmonary vascular tree is affected [4; 5]. Hemodynamically unstable PE (previously referred to as massive or high-risk PE) will result in significant hypotension. Hemodynamic instability is defined as the presence of cardiac arrest requiring resuscitation, or obstructive shock or persistent hypotension not caused by other pathologies [36].

EPIDEMIOLOGY

The annual incidence of PE is difficult to pinpoint but is estimated to be about 60 to 70 cases per 100,000 population [6]. General autopsy studies from all-cause mortality have found PE, variable in number and age, to be present in 30% to 45% of cases [6; 7; 8; 9].

Behind only stroke and coronary artery disease, PE is one of the most common types of cardiovascular disease. It is more common in patients 60 to 70 years of age, with the highest incidence in patients 70 to 80 years of age. Although death following a diagnosis of PE is relatively common, as high as 30%, many of these patients have coexisting serious conditions, such as cancer, recent surgery, or sepsis. The direct mortality associated with undiagnosed/untreated PE during the course of diagnosis and treatment is about 5% to 8%. An estimated 10% of patients with acute PE die suddenly; approximately two-thirds of patients who die from PE do so within two hours of presentation. The mortality rate for those treated for hemodynamically unstable PE is about 20%, and those with cardiogenic shock have a mortality rate of 25% to 30%. Those with a hemodynamically stable PE have a mortality rate of 1% to 25%, depending on the degree of right ventricular dysfunction [2; 4; 5; 10].

PATHOPHYSIOLOGY

What is the most common underlying cause of PE?

Most commonly, a PE occurs when a deep vein thrombus detaches and migrates, or embolizes, into the pulmonary circulation. This can lead to blockage of the pulmonary vasculature, causing a ventilation-perfusion (VQ) mismatch and impairing gas exchange and circulation. PE is more common in the lower lung fields, compared with the upper ones, and both lungs are typically involved. Peripheral PE, as opposed to central PE, can lead to a pulmonary infarction coupled with alveolar hemorrhage. As further obstruction of the pulmonary artery occurs, there is an increase in dead space ventilation and elevation of pulmonary arterial pressure by increasing pulmonary vascular resistance. This further worsens VQ mismatch, with vascular occlusion of the arteries.

Various serum factors are released during a PE formation, including serotonin and thromboxane, which are produced from activated platelets [1; 2; 4]. This induces a cascade of hormonal triggers and related vasoconstriction. Pulmonary arterial pressure increases, which worsens right ventricular afterload and can lead to right ventricular failure and eventually left ventricular system failure. Further clinical progression will lead to a myocardial ischemia due to inadequate coronary circulatory flow, systemic hypotension, and eventual death [1; 4; 5].

DIAGNOSIS

What conditions are included in the differential diagnosis of PE?

A strict (confirmatory) diagnosis of PE would require direct anatomic evidence of pulmonary artery obstruction, which by modern imaging technique (e.g., computed tomography [CT] angiography) would involve invasive measures and exposure to radiation. As the size and distribution (severity) of PE are variable, the preferred strategy for selecting diagnostic testing relies on degree of clinical suspicion, clinical judgment, and assessment of pre-test probability. Selection of noninvasive testing to rule out the diagnosis, based on the assessed clinical probability of PE, has proved effective in reducing the use of CT imaging, thereby minimizing lung and breast-tissue exposure to irradiation [27]. The differential diagnosis includes heart failure, pneumothorax, pneumonia, sepsis, acute chest syndrome, chronic obstructive pulmonary disease (COPD) exacerbation, and anxiety or other psychotropic illnesses. A systematic review and meta-analysis found that a history of sudden dyspnea, syncope, thrombophlebitis, previous deep vein thrombosis, leg swelling, active cancer, or recent surgery was associated with an increased probability of PE [54]. An inability to increase alveolar oxygen pressure (PaO_2) greater than 8.0 kPa (60 mm Hg) despite high-flow oxygen should also raise suspicion for PE.

When a patient does not speak the same language as the clinician, a professional interpreter should be consulted to ensure accurate communication. A retrospective chart review found that, for non-English-speaking patients suspected of having sustained a PE, the positive diagnostic yield of pulmonary angiogram for those who requested an interpreter (7.37%) was nearly double that of those who did not request an interpreter (3.23%) [49].

DIAGNOSTIC WORKUP

Vital Signs

In initial evaluation, vital signs such as blood pressure, heart rate, and rapid estimation of oxygenation by pulse oximetry

are critical to assessing severity of vascular compromise and the stability of the patient. Arterial blood gas (ABG) testing will confirm if a patient has hypoxemia and can be used to obtain the arterial-alveolar gradient to determine if there is a PE or other VQ mismatch [10; 11; 12; 13].

D-dimer Level

Assessment of D-dimer levels can be used for screening purposes and to rule out PE if the pretest probability is intermediate or low. D-dimer is a byproduct of intrinsic fibrinolysis. It is considered to be a highly sensitive test for the absence of PE and has a very high negative predictive value. A normal D-dimer level effectively rules out PE or deep vein thromboembolism. In the event that the d-dimer is elevated, further testing (e.g., computed tomography [CT] angiography, planar VQ scanning) can be performed [10; 14; 15; 16]. Because the test is not specific, an elevated finding is not diagnostic. The specificity of D-dimer decreases with age, and the use of age-adjusted cut-offs is recommended for patients older than 50 years of age. The formula is age (years) x 10 mcg/L for patients older than 50 years of age.

Cardiac Biomarkers

Cardiac biomarker testing may also be useful, particularly as it can identify other diagnoses (e.g., myocardial infarction) [10; 11; 17]. It may help identify signs of right ventricular strain and/or ischemia. An elevated brain natriuretic peptide (BNP) level may indicate right ventricular dysfunction, and higher levels correlate with greater severity of dysfunction.

Various cardiac troponins have also been assessed for diagnostic significance in patients with PE. While these measurements are not diagnostic, elevated troponin is significantly associated with higher mortality in patients with PE [18].

Imaging

Diagnostic imaging is indicated for patients in whom PE cannot be ruled out based on clinical assessment and noninvasive testing. For these patients, CT pulmonary angiography is usually an easily accessible diagnostic imaging modality. It is fast, accurate, and both specific and sensitive. It is also useful for identifying other lung pathology, such as pneumonia and effusions [15; 16]. However, it does require that the patient have good renal function due to the use of iodinated contrast, and it also entails lung and breast-tissue irradiation. Ventilation-perfusion single-photon-emission CT (VQ scan) is a low-radiation option to minimize radiation exposure in younger patients.

Chest x-ray is nonspecific but can help identify pleural effusions and diaphragmatic changes. The classic Westermark sign, which shows a clarified area (loss of vascular markings) distal to a large occluded vessel, and Hampton hump, a dome-shaped, pleural-based opacification, may be present on x-ray. These findings are strongly specific for PE (92% and 82%, respectively) but are not sensitive (14% and 22%, respectively). Chest x-ray can also assist in ruling out pneumonia as part of the differential.

VQ scans visualize areas that are ventilated but not perfused (i.e., VQ mismatch). This testing requires more time, is less specific than CT angiography, and should be done with clinical correlation. However, it is the imaging modality of choice for patients with suspected PE and normal chest x-ray for whom CT angiography is contraindicated, including those with impaired kidney function and pregnant patients. Normal ventilation is 4 L air/minute, and normal perfusion is 5 L blood/minute; thus, a normal VQ ratio is 0.8. A high VQ ratio (>0.8) indicates that the patient's ventilation is exceeding perfusion, while a low VQ ratio indicates a VQ mismatch caused by poor ventilation. When blood is diverted away from the occluded section, overperfusion can occur in the normally ventilated regions. The modified Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED-II) criteria score the probability of PE based on VQ scan findings (***Table 1***).

Duplex ultrasonography for detection of lower extremity venous thrombi is a useful noninvasive test to assess risk and probability in a patient suspected of having PE. It has both high sensitivity and specificity for thrombus [14; 20; 21; 22]. However, a negative test result does not rule out PE, as the thrombus may have dislodged and embolized prior to the testing.

Electrocardiogram

Electrocardiographic signs of right ventricle strain, such as T wave inversions in V1–V4, QR pattern in V1, the S1Q3T3 pattern, and incomplete or complete right bundle-branch block, are useful but insensitive for the assessment of right ventricle dysfunction in acute PE. However, the presence of right ventricular strain on electrocardiogram has been shown to correlate with the extent of pulmonary vascular obstruction and outcomes of acute PE [10; 11; 12; 14; 17; 24].

Echocardiogram

Echocardiography can demonstrate if there was a clot in the right atrium or ventricle and can also be used to show if there are signs of right ventricular dilatation and hypokinesis [12]. When performed, echocardiography has been shown to reduce other testing and lead to more aggressive early therapy [12; 22].

Pulmonary Arteriography

Pulmonary arteriography is a rare test typically performed only on patients with suspected PE for whom CT and chest x-ray are not feasible. It may also be used with cardiac catheterization to assess patients who have chronic thromboembolic pulmonary hypertension to determine if they are good candidates for pulmonary endarterectomy.

GENETIC TESTING

Factor V Leiden (FVL) and prothrombin (PT) genetic variants are associated with an increased risk of future venous thrombosis or PE. Genetic tests for FVL and PT variants are widely available and commonly used. One current use of these tests is to inform decisions regarding anticoagulant medication in order to decrease the risk of future clots (i.e., secondary

MODIFIED PROSPECTIVE INVESTIGATION OF PULMONARY EMBOLISM DIAGNOSIS (PIOPED-II) CRITERIA	
Probability of PE	**Criteria**
High probability	Two or more large mismatched segmental perfusion defects or the arithmetic equivalent of moderate and/or large defects
Normal perfusion or very low probability	No perfusion defects Nonsegmental perfusion defects without other perfusion defects in either lung Perfusion defects smaller than corresponding chest x-ray opacity One to three small subsegmental perfusion defects Two or more matched ventilation and perfusion defects with a regionally normal chest x-ray and some areas of normal perfusion elsewhere Solitary triple-matched defect in a single segment in the middle or upper lung zone Stripe sign Large pleural effusion without other perfusion defects in either lung
Low or intermediate probability	All other findings
Source: [19]	*Table 1*

prevention). The independent Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found enough evidence to recommend against routine testing for FVL and PT gene variants in adults who have idiopathic venous thromboembolism, since longer term preventive treatment with anticoagulant medication offers similar benefits to patients whether or not they have these genetic variations. They also recommend against routine testing for adult family members who do not have a history or symptoms of venous thromboembolism, when the testing is conducted to help decide whether to treat them preventively with anticoagulant medication [50]. However, for patients with venous thromboembolism associated with commonly recognized modifiable risk factors (e.g., contraceptive use, estrogen replacement), genetic testing may help guide preventive treatment decisions.

WELLS CRITERIA	
Clinical Features	**Points**
Clinical symptoms of deep vein thromboembolism	3
Other diagnosis less likely than PE	3
Tachycardia (>100 beats per minute)	1.5
Immobilization for three or more days OR surgery in the past four weeks	1.5
Previous deep vein thromboembolism or PE	1.5
Hemoptysis	1
Malignancy	1
Source: [25]	*Table 2*

CLINICAL SCORING SYSTEMS

The Wells criteria (***Table 2***) and the PE Rule-Out Criteria (PERC) assist clinicians with determining clinical probability for PE [14]. One of the important criteria in the determination of PE is if there is a more likely alternate diagnosis, and this is somewhat subjective. If the Wells criteria are used, a score greater than 6 is considered high probability of PE, 2–6 is moderate probability, and less than 2 is low probability. A modification of the Wells criteria simplifies scoring to either likely (>4) or unlikely (≤4).

The PERC rule was developed for use in emergency care to rule-out PE in patients whose likelihood of PE is low (<15%), so unnecessary diagnostic workups can be avoided. The PERC rule includes [26]:

- Age younger than 50 years
- Heart rate less than 100 beats per minute
- Oxygen saturation of at least 95%
- No prior deep vein thrombosis or PE
- No unilateral leg swelling
- No hormonal estrogen use
- No hemoptysis
- No history of surgery or trauma requiring prior hospitalization in the previous four weeks

If all eight criteria are fulfilled, the patient's risk for PE can be considered sufficiently low and further testing is not necessary [10; 11; 13; 17]. In practice, clinicians tend to overestimate the probability of PE. In cases in which the clinician judges that the patient is very unlikely to have PE but is uncertain whether the estimated likelihood is <15%, the PERC rule or Wells score ≤4 in combination with a normal D-dimer level is reassuring and can be used to safely rule out PE.

TREATMENT

INITIAL MANAGEMENT

The mainstays of initial PE management focus on rapid assessment of clinical severity and stabilization of the patient. As noted, when a patient initially presents, the most critical pieces of information lie in their vital signs (e.g., heart rate, blood pressure, oxygenation). The initial goal for the patient with PE is to maintain oxygen levels. If mechanical circulatory support is required, cardiopulmonary bypass permits right ventricular recovery by decompressing the dilated and dysfunctional ventricle through diversion of the cardiac output to a pump and oxygenator [51]. Alternatively, venoarterial extracorporeal membrane oxygenation (VA-ECMO) functions similarly but is more mobile, allowing for support to be initiated and continued in more diverse settings.

For patients who are hemodynamically unstable, intravenous fluid should be given with caution, because this can lead to right ventricular overload. Hemodynamically stable, low-risk patients should receive anticoagulation alone; those who are at high risk and have hemodynamic compromise may require systemic thrombolysis or surgical- versus catheter-directed therapy. Those who are at intermediate risk have more complicated cases and can be treated with either anticoagulation alone or anticoagulation with potential procedures. As discussed, the risk level will depend on the severity of right ventricular dysfunction on echocardiography, the degree of troponin elevation, the amount of oxygen and vasopressor required, and clot burden and location [10; 11; 12; 13]. The American Society of Hematology (ASH) recommends that patients with PE at low risk for complications be offered home treatment rather than hospital treatment [27].

The therapeutic treatment strategy for patients with a new diagnosis of PE, and venous thromboembolism in general, can be divided into three phases: initial treatment (the first three weeks after diagnosis), primary treatment (three to six months, or longer), and secondary prevention (beginning upon completion of primary therapy and continuing indefinitely) [27]. For primary treatment of patients with PE, whether unprovoked or provoked by a transient or chronic risk factor, the ASH suggests a shorter course of anticoagulation therapy (3 to 6 months) be preferred over a longer course (6 to 12 months). Anticoagulation therapy may be continued indefinitely in select patients for whom the risk for bleeding complications is less than the risk of recurrent PE.

PRIMARY PHARMACOTHERAPY

In selecting initial pharmacotherapy, European guidelines and a 2022 clinical practice review recommend that treatment be guided by risk stratification of PE as high, intermediate, or low based on the patient's clinical presentation [36; 55]. Approximately 5% of patients present with signs of high-risk PE (e.g., shock, end-organ hypoperfusion/dysfunction, blood pressure <90 mm Hg) not caused by arrhythmia, hypovolemia, or intrinsic heart failure [55]. Intermediate-risk patients are those who present with echocardiographic evidence of right heart strain, elevated cardiac biomarkers, or both; those who are hemodynamically stable with normal cardiac biomarkers and no evidence of right ventricular strain are classified as having low-risk PE. Patients classified as having high-risk PE are candidates for initial reperfusion (thrombolytic) therapy; those with intermediate- and low-risk PE should receive immediate anticoagulation therapy [36; 55]. Treatment should be started promptly whenever PE is strongly suspected and the patient's risk of serious bleeding complications is low. Pharmacotherapy options for initial anticoagulation include intravenous unfractionated heparin, subcutaneous low-molecular-weight heparin, subcutaneous fondarinux, factor Xa inhibitors (e.g., apixaban, rivaroxaban), direct thrombin inhibitors (e.g., dabigatran), and intravenous argatropan for patients with heparin-induced thrombocytopenia.

Thrombolytic Therapy

Patients who present with high-risk PE warrant consideration for immediate reperfusion therapy, there being no contraindications (e.g., brain metastases, bleeding disorders, recent surgery) [36; 55]. Intravenous systemic thrombolysis is a readily available option for reperfusion. Thrombolytic agents act to dissolve the thrombus by converting plasminogen into plasmin. With early thrombus resolution, the elevated pulmonary arterial pressure/resistance and accompanying right ventricular dysfunction improve rapidly. Thrombus resolution within the first 24 hours in particular is much faster in thrombolytic therapy than with heparin [52].

The first recombinant tissue plasminogen activator, and the most commonly used thrombolytic agent used in patients with PE, is alteplase (rtPA); other available agents include streptokinase, urokinase, reteplase, and tenecteplase. The main indication for thrombolysis is high-risk PE with thrombus and hemodynamic instability. rtPA is administered at a rate of 50 mg per hour for two hours; the dose should be reduced for patients with weight less than 65 kg. If streptokinase, is used, a loading dose of 250,000 IU is given, followed by and infusion of 100,000 IU per hour for 24 hours. Urokinase is started with a loading dose of 4,400 IU and an infusion of 4,400 IU/kg/hour for 12 hours [29; 52].

According to the American College of Physicians, catheter-directed thrombolytic therapy can be considered if cardiopulmonary deterioration is imminent [53]. There is some evidence that ultrasound-assisted catheter-directed thrombolysis is superior to heparin anticoagulation alone in improving right ventricular dilatation within 24 hours without major bleeding complications or recurrent embolism. Absolute contraindications to thrombolytic therapy include history of intracranial hemorrhage, known structural cerebral vascular lesion, known malignant intracranial neoplasm, recent history (within past three months) ischemic stroke, active bleeding (excluding menses), and recent history (within past three months) significant closed-head trauma or facial trauma [52; 53].

ORAL ANTICOAGULATION THERAPY	
Agent	**Dosage**
Vitamin K Antagonist	
Warfarin	5 mg once daily for most patients[a]
Direct Thrombin Inhibitor	
Dabigatran etexilate	After at least 5 days of initial therapy with a parenteral anticoagulant, transition to oral 150 mg twice daily.
Factor Xa Inhibitors	
Apixaban	10 mg twice daily for 7 days, followed by 5 mg twice daily
Edoxaban	After at least 5 days of initial therapy with a parenteral anticoagulant, transition to once-daily oral 60 mg for patients >60 kg or 30 mg for patients ≤60 kg.
Rivaroxaban	15 mg twice daily with food for 21 days, followed by 20 mg once daily with food
[a]For patients who are expected to be more sensitive to warfarin, a starting dose of 2.5 mg daily is recommended. After three days of treatment, dosage should be adjusted based on INR values.	
Source: [29]	*Table 3*

Oral Anticoagulants

Direct oral anticoagulants (DOACs) (factor Xa inhibitors or direct thrombin inhibitors) are recommended over vitamin K antagonists (e.g., warfarin) for most patients; however, those with renal insufficiency (i.e., creatinine clearance <30 mL/min), moderate-to-severe liver disease, or antiphospholipid syndrome are not good candidates for DOAC therapy [27].

Factor Xa inhibitors such as apixaban and rivaroxaban have the advantage of fixed dosing and no need for monitoring laboratory values, both of which are required of vitamin K antagonists. Rivaroxaban and apixaban do not require any kind of overlap with an intravenous agent. Dose reductions are indicated for those with renal insufficiency. Apixaban can be used in patients with renal insufficiency and is safe for patients on dialysis [2; 28]. Reversal agents are available: idarucizumab for reversal of dabigatran, and andexanet alfa apixaban and rivaroxaban.

The half-life of factor Xa inhibitors is much shorter than the half-life of warfarin. If bleeding develops and requires reversal, a four-factor prothrombin complex concentrate can be used. Direct thrombin inhibitors such as dabigatran can also be used for treatment for these patients. For those with heparin-induced thrombocytopenia, intravenous argatroban or subcutaneous fondaparinux can be used for anticoagulation. The dosage varies according to agent (***Table 3***).

Drug-drug interactions with DOACs are common and may increase risk of bleeding or thrombosis. Important DOAC interactions are often due to medications that affect cytochrome P450 (CYP450) enzymes or transport proteins or increase bleeding propensity.

Warfarin, which used to be the mainstay of therapy, is no longer considered first choice, as the other DOACs have better safety profiles and patient satisfaction. Bleeding is common with warfarin usage and is more likely to be develop in patients who are older (65 years of age and older) and with comorbidities, such as diabetes, recent myocardial infarction, and other chronic conditions (e.g., kidney disease, stroke). If it develops, bleeding can be reversed with vitamin K at a dose of 2.5–10 mg intravenously or orally. Fresh frozen plasma can also be used with elevated prothrombin complex concentrates [5; 30; 31]. Drug interactions are also a concern with warfarin. Another potential complication is warfarin-induced necrosis, which is more likely to occur in patients with a history of heparin-induced thrombocytopenia. If warfarin is used, the dose should be adjusted to reach and maintain a target goal of an international normalized ratio (INR) of 2.5 (range: 2.0–3.0).

Heparin

Intravenous unfractionated heparin has a short half-life and can be reversed with protamine [28]. An initial bolus is given followed by an infusion, during which partial thromboplastin time (PTT) values are monitored. The dosage is based on a weight-based protocol. Although relatively safe to use, the pharmacokinetics of this drug are unpredictable, resulting in the need for close clinical monitoring. However, due to its short half-life, it can quickly be reversed, if needed.

Subcutaneous low-molecular-weight heparin has several advantages, including increased bioavailability and more predictable anticoagulation, as opposed to intravenous unfractionated heparin [28; 32]. There is also decreased incidence of bleeding and potentially better outcomes. Low-molecular-weight heparin is given at a dosage of 1 mg/kg body weight. All heparin products include similar bleeding risk profiles as well as a risk for thrombocytopenia, urticaria, and anaphylaxis. For patients with breakthrough deep vein thrombosis and/or PE during therapeutic warfarin treatment, the ASH suggests using low-molecular-weight heparin over DOAC therapy [27].

Fondaparinux

Fondaparinux is a factor Xa antagonist given subcutaneously in the management of acute PE instead of heparin. Advantages include fixed-dose administration once or twice per day, lack of need for clinical monitoring, and lower risk of thrombocytopenia. The dose is 5 mg for patients who weigh less than 50 kg,

7.5 mg for patients weighing 50–100 kg, and 10 mg for those weighing more than 100 kg. The dose should be adjusted in persons with kidney disease. It is contraindicated for patients with a creatinine clearance less than 30 mL/minute. When used for thromboprophylaxis, some experts recommend a 50% dose reduction or use of low-dose heparin instead [29].

SURGICAL MANAGEMENT

Pulmonary embolectomy is indicated for patients that have high- or intermediate-risk PE with contraindications to thrombolysis; failed thrombolysis or catheter-assisted embolectomy; or hemodynamic shock that is likely to cause death before thrombolysis can take effect [52]. Surgical pulmonary embolectomy is a procedure performed on cardiopulmonary bypass through a midline sternotomy, involving either central or femoral vessel initiation. Management involves moderate hypothermia for better visualization and protection during moments of reduced cardiopulmonary bypass flows. Aortic cross-clamping and cardioplegic arrest are sometimes unnecessary to prevent negative effects on right ventricular recovery [51]. Dual incisions offer improved visualization and better clot extraction. Various methods, such as suction, retrograde perfusion, manual manipulation, or balloon-tipped catheters, can aid clot extraction, but balloon catheters may lead to increased postprocedural complications [51].

SECONDARY PREVENTION

Maintenance anticoagulation for secondary prevention is done for patients who have extensive clot burden or to reduce the risk of new clot formation. There are multiple pharmacotherapeutic options for this phase of treatment, including factor Xa inhibitors (e.g., apixaban), dabigatran, and aspirin. Warfarin and low-molecular-weight heparin are second-line options.

Factor Xa anticoagulants, such as apixaban and rivaroxaban, are the most common first-line option for secondary prevention. Though warfarin was previously used, research has shown a decreased risk for intracranial hemorrhage with factor Xa anticoagulants compared with warfarin. When used for maintenance therapy, the dosage of apixaban is 2.5 mg twice per day; the dosage of rivaroxaban is 10 mg once per day. Cessation of therapy should be considered again after 6 to 12 months [4; 5].

Those with incidental PE, very small clot burdens, and minimal symptoms should likely be treated in an outpatient setting—unless other risk factors are present. However, patients with hemodynamically unstable PE (e.g., extensive clot burden, low blood pressure, abrupt clinical deterioration) often require an intensive care stay.

Aspirin has also been studied for long-term maintenance therapy and is more effective than placebo. However, anticoagulation is typically preferred over aspirin. When anticoagulation therapy is initiated in patients with PE with stable cardiovascular disease who were previously taking aspirin for cardiovascular risk modification, clinicians should consider suspending the aspirin during anticoagulation therapy. Enoxaparin sodium or low-molecular-weight heparin may be used in high-risk cancer patients with recurrent PE [2; 28].

Duration of Pharmacotherapy for Secondary Prevention

How long should anticoagulation therapy continue in patients who have experienced PE?

As noted, the duration of anticoagulation therapy for secondary prevention is dependent on a variety of factors, such as bleeding risk and risk factors for PE, and can range from three months to lifelong therapy [3; 28; 32]. If the patient experienced PE following a transient risk factor (i.e., a provoked event), such as immobilization or recent surgery or trauma, at least three months of treatment is warranted, after which therapy should be reassessed. However, those who have chronic provoked factors for PE, such as active cancer, a hypercoagulable state, or chronic immobility, may benefit from long-term (indefinite) anticoagulation therapy. When creating the treatment plan, the goal is to weigh the benefits of PE and deep vein thrombosis prevention with the risk of anticoagulation events (e.g., bleeding). Risk factors for bleeding include age 65 years or older, frequent falls, alcohol abuse, renal failure, previous stroke, diabetes, and anemia.

For patients who develop PE provoked by a transient risk factor and who have a history of a previous thrombotic event also provoked by a transient risk factor, the ASH guideline panel suggests stopping anticoagulation after completion of the primary treatment phase of therapy [27].

PE IN THE OUTPATIENT SETTING

When possible, patients at assessed low risk for complications (i.e., minimal risk of PE-related death) should be discharged from the hospital and continue to receive treatment at home. Such patients are hemodynamically stable, with have no right heart strain and normal cardiac biomarkers. Most patients with low-risk PE can be treated with an oral anticoagulant or a brief period of low-molecular-weight heparin followed by oral therapy. The presence or absence of comorbidities and proper care and anticoagulation therapy, which can be provided on an outpatient basis, should be noted. Scoring systems have been developed to stratify these patients, including the HESTIA rule (***Table 4***), the PE Severity Index (PESI), and its simplified version (sPESI) (***Table 5***) [33; 34; 35].

The PESI scales identify those with a low risk of 30-day mortality [33]. The criteria used include age, sex, history of cancer, history of chronic pulmonary disease, heart rate, systolic blood pressure, and oxygen saturation [33]. The scales relate the risk stratification score to an associated 30-day mortality and risk of death and can assist in identifying patients who may appropriately be managed at home. The patient's social situation, access to supportive care, and ability to transfer to higher level care should all be considered before shifting to outpatient management.

HESTIA EXCLUSION CRITERIA FOR OUTPATIENT TREATMENT	
Criteria	**Points[a]**
Hemodynamically unstable	1
Thrombolysis or embolectomy needed	1
Active bleeding or high risk of bleeding	1
More than 24 hours on supplemental oxygen needed to maintain oxygen saturation >90%	1
PE diagnosed during anticoagulant treatment	1
Severe pain requiring IV pain medication for more than 24 hours	1
Medical or social reason for hospital treatment for more than 24 hours (e.g., infection, malignancy, no support system)	1
Creatinine clearance of <30 mL/min	1
Severe liver impairment	1
Pregnancy	1
History of heparin-induced thrombocytopenia	1
[a]A score of 1 or more is defined as high risk and rules out outpatient treatment.	
Source: [36]	*Table 4*

THE ORIGINAL PULMONARY EMBOLISM SEVERITY INDEX (PESI) AND THE SIMPLIFIED PESI (S-PESI) CLINICAL RISK SCORES		
Parameter	**PESI**	**s-PESI**
Age	Age in years	1 if older than 80 years
Male sex	10	—
Cancer diagnosis	30	1
Chronic heart failure Chronic pulmonary disease	10 10	1
Pulse ≥110 beats per minute	20	1
Systolic blood pressure <100 mm Hg	30	1
Respiratory rate ≥30 breaths per minute	20	—
Temperature <36°C	20	—
Altered mental status	60	—
Arterial oxyhemoglobin saturation <90%	20	1
Risk Stratification (PESI)		
Class I (≤65 points)	Very low 30-day mortality risk (0% to 1.5%)	
Class II (66–85 points)	Low mortality risk (1.7% to 3.5%)	
Class III (86–105 points)	Moderate mortality risk (3.2% to 7.1%)	
Class IV (106–125 points)	High mortality risk (4% to 11.4%)	
Class V (>125 points)	Very high mortality risk (10% to 24.5%)	
s-PESI Score		
0 points	30-day mortality risk 1%	
1 or more points	30-day mortality risk 10.9%	
Source: [37; 56; 57]		*Table 5*

Anticoagulation options to manage confirmed PE in an outpatient setting include subcutaneous low-molecular-weight heparin, fondaparinux, unfractionated heparin, or DOACs [28; 32; 38; 39]. The treatment duration is generally three to six months [38; 39]. Following the initial three-month period, the decision of whether or not to continue treatment will be made based on continued risk of recurrent thromboembolic balanced against the risks of continued anticoagulation [4; 5; 40].

PE AND COVID-19

Hospitalized patients with advanced COVID-19 may have laboratory signs of a coagulopathy and increased risk for arterial and venous thromboembolic complications, including PE [41; 42; 43]. The pathogenesis is unknown but likely involves some combination of systemic inflammation, endothelial dysfunction, platelet activation, immobility, and stasis of blood flow [43]. The earliest abnormalities are elevated D-dimer levels and mild thrombocytopenia; with disease progression, fibrin degradation products are elevated and prothrombin time becomes prolonged. Laboratory measure of coagulation factors in patients hospitalized with COVID-19 provides a way to track disease severity. The presence of an elevated D-dimer on admission carries a poor prognosis and has been associated with increased risk of requiring mechanical ventilation, intensive care unit admission, and mortality [43; 44]. The most frequently reported complications of COVID-19 coagulopathy are deep venous thrombosis and PE. In a prospective study of 150 critically ill patients from two centers in France, 25 patients developed PE and 3 developed deep vein thrombosis, despite prophylactic anticoagulation [45]. In a report of 184 patients with severe COVID-19 from three centers in the Netherlands, the cumulative incidence of venous thromboembolism was 27%, including PE in 80% of the cases affected [46]. Other centers have reported lower rates. Among 393 patients from New York, venous thromboembolism was diagnosed in only 13 patients (3.3%), 10 of whom were on mechanical ventilation [47]. The National Institutes of Health recommends all hospitalized patients with COVID-19 who experience rapid deterioration of pulmonary, cardiac, or neurological function or sudden, localized loss of peripheral perfusion be evaluated for thromboembolic disease [48].

At present, there are limited data available to inform clinical management around prophylaxis or treatment of venous thromboembolic complications in patients with COVID-19 [41]. One source of interim guidance recommends regularly monitoring hemostatic markers—namely D-dimer, prothrombin time, and platelet count—in all patients presenting with COVID-19 and prophylactic use of low-molecular-weight heparin in all hospitalized patients, unless there are contraindications [43]. The National Institutes of Health recommends that hospitalized, nonpregnant adults with COVID-19 who do not require intensive-level care and have no evidence of venous thromboembolism receive a therapeutic dose of heparin if their D-dimer levels are above the upper normal limit and they require low-flow oxygen, as long as they do not have an increased risk of bleeding [48].

Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include [48]:

- Platelet count <50 x 10^9/L
- Hemoglobin <8 g/dL
- Need for dual antiplatelet therapy
- Bleeding within the past 30 days that required an emergency department visit or hospitalization
- History of a bleeding disorder or an inherited or active acquired bleeding disorder

Low-molecular-weight heparin is preferred over unfractionated heparin because of its ease of administration and because low-molecular-weight heparin was the predominant form of heparin used in the clinical trials for COVID-19 [48].

In patients without venous thromboembolism who have started treatment with therapeutic doses of heparin, treatment should continue for 14 days or until they are transferred to intensive care or discharged from the hospital, whichever comes first. A prophylactic dose of heparin is also recommended for patients who do not meet the criteria for receiving therapeutic heparin or are not receiving a therapeutic dose of heparin for other reasons, unless a contraindication exists [48].

For those patients who develop a PE in the setting of a COVID-19 infection, about 50% will report persistent fatigue, reduced exercise tolerance, and dyspnea [14; 23]. Of these patients, one-half will also have signs of right ventricular dysfunction on echocardiogram after the diagnosis is made, referred to as post-PE syndrome. This further leads to dyspnea on exertion, damage to the venous valves in the leg, prolonged lower extremity swelling and aching, venous ulcers, and impaired quality of life.

CONCLUSION

PE is a common cause of acute-onset breathlessness and chest pain, often confused for many other diagnoses. It should remain on one's clinical differential due to the fact that it can be life-threatening and is treatable if caught and managed early. A variety of treatment options are at the forefront for ensuring that patients are given the best possible outcome.

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

Substance Use Disorders and Pain Management

Includes 8 Pharmacotherapeutic/Pharmacology Hours

This course meet the Michigan requirement for pain and symptom management and opioid/controlled substance education

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

Audience

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

Course Objective

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

Learning Objectives

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

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

Faculty

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

Faculty Disclosure

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

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Division Planner/Director Disclosure

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This activity was planned by and for the healthcare team, and learners will receive 8 Interprofessional Continuing Education (IPCE) credits for learning and change.

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

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INTRODUCTION

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

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

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

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

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

SUBSTANCE USE DISORDER SCREENING AND DIAGNOSIS

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

RISK FACTORS

What are risk factors for the development of a substance use disorder?

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

Genetic Predisposition

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

Children with Conduct Problems

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

Stress and Distress

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

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

Other Mental Disorders

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

Environmental Stimuli

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

SCREENING

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

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

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

DIAGNOSIS

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

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

- Tolerance
  - Need for increased doses of the substance for the desired effect
  - A markedly diminished effect with continued use of the same amount
- Withdrawal

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

SUBSTANCE USE DISORDER TREATMENT

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

TREATMENT PLANNING

Assessing Readiness to Change

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

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

Motivational Interviewing

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

PSYCHOSOCIAL THERAPY

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

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

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

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

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

Contingency Management

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

The goal of contingency management interventions is to increase the opportunity cost of substance use by arranging an environment where drug use results in the forfeiture of a predetermined item or privilege, referred to as an alternate reinforcer [23]. Treatment with a contingency management component was first used with cocaine-abusing methadone patients, a highly suitable population for two reasons: cocaine abuse is prevalent among patients with opioid use disorder

receiving methadone maintenance, and methadone patients are required to report to the clinic daily to receive their medication under staff supervision. Daily clinic appointments are often considered a significant constraint on employment, travel, and other activities. Patients who are able to abstain from drugs of abuse, as measured by a urine drug screen, may be allowed several days of take-home methadone doses, which can act as a behavioral contingent [24]. Several studies have shown that this contingent condition has led to greater treatment retention and reductions in cocaine use than those found in comparison treatment conditions, although this effect dissipates with longer-term follow-up [22; 25; 26; 27].

Community Reinforcement

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

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

Motivational Interventions

Motivational interventions for substance use disorders stem from the theory that targeting and enhancing motivation to quit drugs will increase positive outcome; positive outcome is increased when motivation comes internally rather than when it is externally imposed. Specifically, motivational enhancement therapy is based on the Transtheoretical Stages of Change Theory, which postulates that patients pass through a series of stages of thought, planning, and action in the process of behavior change [30]. Motivational enhancement therapy is intended to enhance motivation and commitment to change, activate patient resources, and facilitate movement along the readiness-to-change spectrum [31]. Motivational enhancement therapy helps patients build internal motivation through the resolution of issues related to ambivalence. The therapeutic approach is characterized by nonconfrontive, nonjudgmental interviewing that helps the patient consider the pros and cons of change. Motivational enhancement therapy also strives to enhance patient self-efficacy [30]. Motivational enhancement therapy seems to be more effective in patients with low initial levels of motivation when used for patients with substance use disorder. It tends to result in less relapse to use and fewer total days of use [32].

Coping and Social Skill Training

What are the primary areas addressed by coping and social skill training (CSST)?

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

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

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

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

Drug Counseling

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

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

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

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

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

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

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

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

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

PHARMACOTHERAPY FOR DETOXIFICATION AND ABSTINENCE

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

Alcohol Use Disorder

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

Disulfiram

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

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

BID = two times per day, DEA = Drug Enforcement Administration, IM = intramuscular, IV = intravenous, PO = oral, SL = sublingual, SQ = subcutaneous, TID = three times per day.

Source: [39] *Table 2*

Due to more modern and improved medication modalities, many clinicians prescribe disulfiram as a last-resort intervention. Although widely used, it is less clearly supported by clinical trial evidence [43; 44; 45].

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

Naltrexone

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

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

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

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

Acamprosate

Acamprosate (Campral) is a synthetic compound that has a chemical structure similar to that of the naturally occurring amino acid neurotransmitters taurine and gamma-aminobutyric acid (GABA) [39]. Because chronic alcohol use is associated with decreased GABA and glutamate activity, a hyperexcitable glutamate system is one possible alcohol withdrawal mechanism. Glutamate systems may become unstable for 12 months after a person stops drinking. In a review of published, double-blind, placebo-controlled clinical trials evaluating the safety and efficacy of acamprosate in the treatment of alcohol use disorder, Mason reported that acamprosate appeared to improve treatment completion rate, abstinence rate and/or cumulative abstinence during treatment, and time to first drink, than placebo [53]. The effect on abstinence, combined with an excellent safety profile, lend support to the use of acamprosate across a broad range of patients with alcohol use disorder [54]. It is important to note that medication in combination with therapies can improve outcomes.

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

Due to risk of diminished renal function in patients 65 years of age and older, baseline and frequent renal function tests should be performed in this population. Dose reductions also may be necessary [41].

Baclofen

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

Anticonvulsants

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

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

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

Opioid Use Disorder

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

Crisis Intervention

Which drug is considered the criterion standard in reversing respiratory depression and coma in acute opioid overdose?

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

Harm Reduction

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

Detoxification

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

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

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

Agonist Replacement Therapy

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

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

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

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

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

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

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

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

Tobacco Use Disorder

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

Bupropion

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

Varenicline Tartrate

Another effective non-nicotine therapy for smoking cessation is varenicline tartrate, a partial agonist selective for nicotine acetylcholine receptor subtypes. Released in 2006, varenicline is available in monthly dose packs (0.5 mg and 1 mg tablets) and is approved for a 12-week course of treatment [82]. Patients able to quit smoking may continue the therapy for an additional 12 weeks for increased likelihood of long-term cessation and even up to a year in certain cases, to prevent relapse; however, medication should be stopped and patients should be reassessed if the intervention has not led to smoking cessation within the initial 12 week timeframe [39; 87; 88]. Clinical trials reveal that varenicline may be favorable to bupropion for abstinence (44% versus 30%); the medication has also been shown to help at least 20% of patients remain smoke-free for up to one year [89; 90]. Recognizing that cessation success rates increase when pharmacologic and behavioral therapies are combined, the manufacturer urges patients to combine use of varenicline with a behavioral support plan. Co-administration of varenicline and transdermal nicotine may exacerbate incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue. One study found varenicline alone to be more effective than other treatment options, while a meta-analysis study found that combination therapy (varenicline and NRT) was more effective than varenicline alone [91; 92]. In 2021, the manufacturer of Chantix, a brand of varenicline, halted production of varenicline due to unacceptably high levels of nitrosamines; however, this issue was considered resolved by May 2022 [93]. In addition, all lots of 0.5-mg and 1-mg tablets of Chantix were subject to a voluntary recall. However, the FDA does not recommend that patients halt use of varenicline, and generic formulations and other brands remained available.

Other Options

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

POLYSUBSTANCE USE

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

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

- FDA-approved pharmacotherapy together with counseling to treat:
  - Alcohol and cocaine dependence
  - Cocaine and opioid dependence

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

CO-OCCURRING MENTAL DISORDERS

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

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

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

Assessment

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

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

Treatment Approach

What should be the initial focus of treatment of comorbid mental and substance use disorders?

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

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

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

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

FACTORS IMPACTING RECOVERY

Stigma

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

Trauma

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

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

Social Determinants of Health

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

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

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

LEGAL AND ETHICAL ISSUES IN THE TREATMENT OF SUBSTANCE USE DISORDERS

Which ethical issue should be considered when caring for patients with substance use disorders?

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

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

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

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

PAIN MANAGEMENT AND SUBSTANCE MISUSE

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

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

PAIN MANAGEMENT APPROACHES

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

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

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

Acute Pain

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

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

Chronic Pain

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

Implantable intrathecal opioid infusion and/or spinal cord stimulation may be options for severe, intractable pain. Both options require that devices or ports be implanted, with associated risks. With intrathecal opioid infusion, the ability to deliver the drug directly into the spine provides pain relief with

significantly smaller opioid doses, which can help to minimize side effects (e.g., drowsiness, dizziness, dry mouth, nausea, vomiting, and constipation) that can accompany systemic pain medications that might be delivered orally, transdermally, or through an IV [131]. However, use of opioid infusion has traditionally been limited to cancer pain. With spinal cord stimulation therapy, the most challenging aspect is patient selection. In order for patients to be considered for spinal cord stimulation, other options should have been ineffective or be contraindicated. Spinal cord stimulation is indicated for severe neuropathic pain persisting at least six months.

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

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

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

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

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

Palliative Care and Pain at the End of Life

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

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

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

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

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

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

Encouraging patients to be honest about pain and other symptoms is also vital. Clinicians should ensure that patients understand that pain is multidimensional and emphasize the importance of talking to a member of the healthcare team

about possible causes of pain, such as emotional or spiritual distress. The healthcare team and patient should explore psychosocial and cultural factors that may affect self-reporting of pain, such as concern about the cost of medication.

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

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

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

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

CREATING A TREATMENT PLAN AND ASSESSMENT OF ADDICTION RISK

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

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

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

If substance abuse is active, in remission, or in the patient's history, consult an addiction specialist before starting opioids [132]. In active substance abuse, do not prescribe opioids until the patient is engaged in treatment/recovery program or other arrangement made, such as addiction professional co-management and additional monitoring. When considering an opioid analgesic (particularly those that are extended-release or long-acting), one must always weigh the benefits against the risks of overdose, abuse, addiction, physical dependence and tolerance, adverse drug interactions, and accidental exposure by children [125; 127; 134].

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

Risk Assessment Tools

Opioid Risk Tool (ORT)

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

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

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

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

Screening Instrument or Substance Abuse Potential (SISAP)

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

CAGE and CAGE-AID

What does the CAGE acronym stand for?

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

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

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

Considerations for Pain Management in Patients with Comorbid Opioid Use Disorder

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

Informed Consent and Treatment Agreements

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

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

Periodic Review and Monitoring

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

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

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

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

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

Involvement of Family

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

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

Assessment Tools

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

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

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

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

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

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

Urine Drug Tests

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

Initially, testing involves the use of class-specific immunoassay drug panels [132]. If necessary, this may be followed with gas chromatography/mass spectrometry for specific drug or metabolite detection. It is important that testing identifies the specific drug rather than the drug class, and the prescribed

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

opioid should be included in the screen. Any abnormalities should be confirmed with a laboratory toxicologist or clinical pathologist. Immunoassay may be used point-of-care for "on-the-spot" therapy changes, but the high error rate prevents its use in major clinical decisions except with liquid chromatography coupled to tandem mass spectrometry confirmation.

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

Concurrent Use of Benzodiazepines

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

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

Consultation and Referral

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

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

Medical Records

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

Patient Education on the Use and Disposal of Opioids

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

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

- Product-specific information
- Taking the opioid as prescribed
- Importance of dosing regimen adherence, managing missed doses, and prescriber contact if pain is not controlled
- Warning and rationale to never break or chew/crush tablets or cut or tear patches prior to use
- Warning and rationale to avoid other central nervous system depressants, such as sedative-hypnotics, anxiolytics, alcohol, or illicit drugs
- Warning not to abruptly halt or reduce the opioid without physician oversight of safe tapering when discontinuing

- The potential of serious side effects or death
- Risk factors, signs, and symptoms of overdose and opioid-induced respiratory depression, gastrointestinal obstruction, and allergic reactions
- The risks of falls, using heavy machinery, and driving
- Warning and rationale to never share an opioid analgesic
- Rationale for secure opioid storage
- Warning to protect opioids from theft
- Instructions for disposal of unneeded opioids, based on product-specific disposal information

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

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

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

Discontinuing Opioid Therapy

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

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

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

Considerations for Non-English-Proficient Patients

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

IDENTIFICATION OF DRUG DIVERSION/SEEKING BEHAVIORS

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

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

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

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

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

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

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

INTERVENTIONS FOR SUSPECTED OR KNOWN ADDICTION OR DRUG DIVERSION

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

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

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

When dealing with patients suspected of drug seeking/diversion, first inquire about prescription, over-the-counter, and illicit drug use and perform a thorough examination [161]. Pill counting and/or UDT may be necessary to investigate possible drug misuse. Photo identification or other form of identification and social security number may be required prior

to dispensing the drug, with proof of identity documented fully. If a patient is displaying suspicious behaviors, consider prescribing for limited quantities.

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

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

COMPLIANCE WITH STATE AND FEDERAL LAWS

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

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

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

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

Controlled Substances Laws/Rules

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

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

State-Specific Laws and Rules

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

CONCLUSION

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

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

Pharmacologic and Medical Advances in Obesity Management

Includes 12 Pharmacotherapeutic/Pharmacology Hours

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

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

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

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

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

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

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.

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.

Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency, and California Assembly Bill 241, Implicit Bias.

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

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

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.
- 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].

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*

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. Fol-

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

Source: [41] *Table 2*

lowing 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 preva-

lence increased with educational attainment. No differences in obesity prevalence by education level were noted among non-Hispanic Asian women and men or Hispanic men [43].

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

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

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

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

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

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

Military-Aged Population

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

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

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

Pediatric Population

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

INCIDENCE

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

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

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].

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

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

Source: [42] *Table 3*

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

Source: [45] *Table 4*

PERSONAL AND SOCIETAL BURDEN OF OBESITY

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

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

Excessive body fat is a cause of 13 cancers, including esophageal, gastric, cardiac, colorectal, liver, gallbladder, pancreas, meningioma, postmenopausal breast, endometrium, ovary, kidney, thyroid, and multiple myeloma [47]. A 5-point increase in BMI is strongly associated with increased risk of thyroid and colon cancers in men, endometrial and gallbladder cancers in women, and esophageal adenocarcinoma and renal cancers in both sexes [46]. From 2004 to 2015, the prevalence of these cancers increased 7% while cancers not known to be related to excessive body fat decreased 13% [46]. Overweight- and

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*

obesity-related cancers account for about 40% of all cancers. With approximately 70% of adults overweight or obese, promoting the maintenance of weight loss to decrease cancer risk is critical [47].

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

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

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

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

MORTALITY

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

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

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

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

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

ETIOLOGY OF THE OBESITY EPIDEMIC

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

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

DIET, PHYSICAL ACTIVITY, AND BMI

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

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

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

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

Macronutrient Intake and BMI: 1965–2011

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

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

Dietary Changes: 1999–2016

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

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

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

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

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

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

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

Weight Loss Attempts: 1999–2016

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

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

ENERGY EXPENDITURE RESEARCH

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].

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,

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*

in favor of nonsteroidal anti-inflammatory drugs (NSAIDs) and DMARDs [131].

PRIORITIZATION FOR PATIENTS WITH OBESITY AND CARDIOMETABOLIC DISEASE

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

TREATING TO TARGET WITH ANTIOBESITY MEDICATIONS

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

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

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

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

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

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

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

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

ANTIOBESITY MEDICATIONS

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

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

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

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

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

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

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

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

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

INDICATIONS FOR USE

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

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

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

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

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

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].

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 conclu-

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*

sions 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].

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].

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*

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

Demand and Supply Problems

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

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

Off-Label Prescribing of Antiobesity Medications

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

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

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.

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*

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

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

TERMINOLOGY

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

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

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

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

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

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

PROPOSED MECHANISMS

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

MBS is traditionally classified as restrictive, malabsorptive, or restrictive plus malabsorptive (e.g., BPD/DS) [208]. Historically, macronutrient malabsorption and restriction were considered necessary for efficacy [200; 209]. However, RYGB and sleeve gastrectomy produce large and sustained weight

loss despite lower malabsorption. The weight-loss efficacy of both likely involve normal physiological mechanisms affecting energy intake, expenditure, and metabolic regulation, significantly mediated by increased GLP-1 signaling and also by melanocortin signaling pathways, which clearly go beyond mechanical restriction and malabsorption [200].

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

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

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

INDICATIONS FOR BARIATRIC SURGERY

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

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

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

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. Systematic reviews and meta-analyses of these interventions have concluded their efficacy in preventing or reversing weight recurrence is marginal or null [224].

Intervention for patients experiencing nonresponse or weight recurrence entails revisional surgery or adjuvant antiobesity medication [126]. Because most revisional procedures carry higher morbidity than primary procedures, nonsurgical interventions should be tried first [224; 255].

Antiobesity Medication

Antiobesity medications may work synergistically with MBS, and treating patients with obesity via a multimodal approach has the potential to increase and possibly enhance MBS efficacy and durability. The ASMBS supports preoperative use of antiobesity medications for reducing perioperative risk and increasing postsurgery attainment of weight-loss goals and comorbidity resolution as well as post-MBS for ameliorating weight recurrence [124].

Phentermine is one of the most commonly used antiobesity medications in MBS patients. Pairing phentermine with topiramate may be advantageous in weight-loss efficacy through

combinatory mechanisms and cost considerations in post-MBS patients. GLP-1 agonists offer high efficacy, few drug interactions, and few side effects, but cost can be a deterrent [124].

In most patients, MBS results in supraphysiological levels of circulating GLP-1. However, patients with poor postsurgery weight loss demonstrate an unfavorable postoperative gut hormone profile, including lower circulating GLP-1 levels. As such, GLP-1 analogs may benefit these patients [256].

In the BARI-OPTIMISE randomized placebo-controlled trial, patients with poor weight loss (≤20%) and suboptimal nutrient-stimulated GLP-1 response one or more years following sleeve gastrectomy or RYGB received liraglutide 3.0 mg or placebo. After 26 weeks, mean total weight loss with liraglutide was 8.82%, compared with 0.54% with placebo [256].

Patients receiving liraglutide for late weight recurrence after RYGB were prospectively followed. After 24 months, patients lost >85% of weight recurrence from nadir; hypertension and dyslipidemia also improved [257].

Weight recurrence studies of GLP-1 RAs have largely used liraglutide. However, semaglutide may be superior to liraglutide for weight recurrence, regardless of MBS procedure. In one study, semaglutide was superior on with 12-month weight loss (13% vs 9%) and odds ratio for ≥15% weight loss (2.55) compared with liraglutide [258].

Patients treated with liraglutide or semaglutide for weight recurrence after RYGB lost 67.4% of the weight regain after six months. More patients on semaglutide had total weight loss ≥10% (47.6% vs 31%) and ≥15% (24% vs 3.5%) [254].

The optimal time to initiate antiobesity medication may be at weight plateau, rather than after weight recurrence [259]. Proactive liraglutide may significantly augment ESG efficacy. Initiated five months after ESG and assessed seven months later, liraglutide/ESG showed greater reductions in weight (25% vs 20.5%) and body fat (10.5% vs 8%) compared with ESG alone at one year postprocedure [260].

Revisions/Conversions

The choice of conversion depends on the type of primary operation and the indication for conversion [125]. Patients may require reoperation (to correct/adjust) or conversion following any primary MBS, but some evidence suggests that more "restrictive" procedures (e.g., LAGB, sleeve gastrectomy) lead to higher rates of reoperation or conversion.

Conversions are the third most common MBS procedure. Of 57,683 performed between 2015 and 2017, most involved gastric band (LAGB) conversion to sleeve gastrectomy (15,433), to RYGB (10,485), or removal (14,715). It is projected that sleeve gastrectomy to RYGB conversions (8,491) will likely surpass LAGB conversions with time [261].

Weight recurrence within several years of sleeve gastrectomy is described as an emerging problem. After seven years, 28% to 30% of patients had weight recurrence and 20% had revisions, mostly due to weight recurrence (13%) and GERD (3%) [262; 263]. However, over 5 to 12 years after RYGB, up to 25% of patients experience <20% weight loss due to nonresponse/weight recurrence [256].

The ASMBS has made several suggestions concerning revisions/conversions, stating that in addition to improving weight loss, type 2 diabetes improvement and remission rates also increase [125]. It is important to consider behavioral factors, such as binge-eating, may be responsible for poor weight outcomes after LAGB reoperation. If necessary, conversions to RYGB or sleeve gastrectomy after LAGB can be performed in one or two stages. If conversion is required due to GERD, the preferred procedure is RYGB. Conversion of sleeve gastrectomy for additional weight loss can be RYGB or duodenal switch, which results in greater weight loss than RYGB but higher risk of long-term nutritional deficiencies [125].

For weight recurrence after sleeve gastrectomy, SADI-S led to greater total weight loss (30% vs 19%) and remission of type 2 diabetes and hypertension, fewer complications and reoperations after five years when compared with OAGB [264]. In one trial, OAGB for 1,075 patients with weight recurrence after various MBS led to two- and five-year excess weight loss of 68.5% and 71.6%, respectively. Adverse events included leak (1.5%), marginal ulcer (2.4%), anemia (2%), and mortality (0.3%) [265].

CONCLUSION

During 1980–2000, obesity prevalence increased roughly 100% as adults consumed less fat and sugar, became more active, and initiated more frequent weight loss attempts with diet and exercise. The obesity epidemic is unexplained by worsening diet and physical inactivity.

Today, it is acknowledged that obesity is a chronic, relapsing disease with cardiometabolic complications (e.g., insulin resistance, hypertension, type 2 diabetes, NAFLD, cardiovascular diseases) arising from adipose mass due to shared pathophysiology. The goal of obesity treatment—long-term weight loss sufficient to ameliorate cardiometabolic morbidity and premature mortality—usually requires antiobesity medications, bariatric surgery, or both.

Recently approved and emerging antiobesity medications are revolutionizing obesity treatment by achieving long-term weight loss previously unattainable without surgical intervention. Reversing the low utilization of medication and surgical treatment begins with ending the stigmatization of patients with obesity.

APPENDIX: PHYSIOLOGY AND PATHOPHYSIOLOGY

As explored throughout this course, knowledge of the mechanisms underlying obesity and advances in the understanding of how and why adiposity persists are essential in the development of new approaches in the treatment of patients with obesity. Healthcare professionals involved in the care of these patients benefit from a clear understanding of the physiology and pathophysiology involved.

NEUROHORMONAL REGULATION OF ENERGY BALANCE AND BODY WEIGHT

The biological system that regulates energy balance and body weight is dominated by a bidirectional feedback loop between the brain and periphery, sometimes called the gut-brain axis [108]. Peripheral tissue (gut, pancreas, adipose tissue) releases hormones, metabolites, and peptides to communicate information about long-term energy stores and short-term nutrient availability to the brain. Because these molecular messengers provide homeostatic feedback of energy availability and status to the brain, they are called signals (of satiety, hunger, adiposity) [266].

These signals of energy balance reach the hypothalamus via the bloodstream and/or the brainstem via afferent vagal pathways that terminate in the nucleus tractus solitarius (nTS) [103; 267]. Brain circuits respond to this input by adjusting metabolism and behavior to acute and long-term needs and modifying energy intake and expenditure to match energy demands. Over time, this homeostatic regulation of energy balance establishes a metabolic set-point [101; 102].

Peripheral signals can be anorexigenic (appetite-suppressing) or orexigenic (appetite-stimulating) and long- or short-term. Long-term signals of energy balance circulate in proportion to fat mass to inform the brain about long-term energy storage in adipose tissue (i.e., adiposity signals) and are always (leptin) or often (insulin) anorexigenic. Short-term signals of nutrient and meal-derived energy availability (i.e., satiety and hunger signals) are gut-released and include [101; 150; 267]:

- Glucagon-like peptide-1 (GLP-1), peptide YY (PYY), glucose-dependent insulinotropic polypeptide (GIP), cholecystokinin (CCK), and oxyntomodulin (OXM), which are all anorexigenic
- Ghrelin, which is orexigenic and known as the "hunger hormone"

In obesity, this system is dysfunctional and generates and sustains excessive adipose tissue mass. Abnormal interaction between peripheral hormones and brain centers of energy homeostasis is a core feature of obesity pathophysiology [3].

The Hypothalamus

The hypothalamus, as the superordinate regulator of energy homeostasis, receives input via the bloodstream, ascending neurons from the brainstem, and descending neurons from cortical areas. It then coordinates energy balance and other homeostatic systems, integrates reciprocal orexigenic and anorexigenic responses, and governs metabolic adaptation [102; 103; 268].

The arcuate nucleus (ARC) of the hypothalamus is adjacent to the median eminence, a circumventricular organ outside the blood brain barrier, giving ARC neurons direct bloodstream access to detect circulating hormones and metabolites. Arcuate neurons are thus 'first-order' neurons, since circulating peripheral signals act directly on them [101; 102; 269].

First-order ARC neurons project to second-order neurons in the paraventricular (PVH), ventromedial, dorsomedial, and lateral hypothalamus. Second-order hypothalamic neurons project to brainstem circuits and midbrain areas [101; 102; 115; 269]. Brainstem circuits respond rapidly to gut signals to control meal size and termination. Brainstem neurons project to hypothalamic areas and communicate to the gut via parasympathetic signals. Many antiobesity medications work by activating receptors on both hypothalamic and brainstem neurons [102; 115].

The hypothalamic integrative capacity is enhanced by crosstalk with corticolimbic systems that process external sensory information, cognitive and emotional control, and reward-based decision making and mediate emotional, cognitive, and executive aspects of ingestive behavior [8].

A salience network in the frontal cortex, ventral and dorsal striatum, and amygdala, associated with motivation, desire, and craving for palatable high-energy food, is more active in obese than lean subjects. An inhibitory network in the dorsolateral prefrontal cortex is activated in subjects instructed to resist craving. This cognitive control ability is greater in patients with the highest weight loss after bariatric surgery. Connectivity between the salience and inhibitory networks (hedonic control) and the hypothalamus (homeostatic control) differs in lean versus obese subjects. The former homeostatic/hedonic ingestive dichotomy has given way to a more unified and integrative control system [8].

The Arcuate Nucleus and the Melanocortin System

In the ARC, the melanocortin system is a critical and conserved pathway of body weight homeostasis and essential to the regulatory function of the hypothalamus in energy balance and homeostasis. The melanocortin system consists of two distinct, functionally antagonistic neuron populations [150; 268; 270; 271; 272]:

Anorexigenic melanocortin neurons (POMC), which release melanocortin peptides (α- and β-MSH) that bind and stimulate melanocortin receptors (MC3R and MC4R) expressed on second-order neurons. Brain-derived neurotrophic factor, corticotropin-releasing hormone, and thyrotropin-releasing hormone mediate the downstream effects of MC4R activation on suppressing food intake.

Orexigenic agouti-related protein (AgRP) neurons, which antagonize melanocortin neurons and receptors by releasing AgRP, gamma-aminobutyric acid (GABA), and neuropeptide Y (NPY). AgRP antagonizes MC3/4R to prevent the anorexigenic effects of α- and β-MSH binding. GABA directly inhibits POMC neurons in the ARC. NPY is the most potent known short-term orexigenic stimulus.

The brainstem has a smaller number of POMC neurons. AgRP neurons solely exist in ARC and send long-distance projections throughout the hypothalamus and brainstem. AgRP neuron expression is negatively correlated with BMI [273].

POMC and AgRP neurons are tightly linked, exert opposite functions in the reciprocal regulation of downstream MC3/4R neurons, and are themselves reciprocally regulated by circulating hormones and neural inputs [274; 275].

Energy Balance and Melanocortin Activity

POMC and AgRP neurons detect and respond to circulating metabolic and hormone signals of short- and long-term deficit or surplus in energy availability [8]. Circulating hormones (e.g., leptin, insulin, ghrelin, GLP-1) bind to their respective receptors (LepR, InsR, GHSR, GLP-1R) on POMC and AgRP neurons [141]. Energy surplus stimulates POMC neurons. Heightened energy demand activates AgRP neurons [3; 276].

The PVH is a major output nucleus for the ARC and receives afferent inputs from POMC and AgRP neurons [102]. It has the highest number of MC4R-expressing neurons in the CNS [271].

POMC neurons are stimulated by positive energy balance, elevated leptin, and insulin. In contrast, AgRP neurons are inhibited by leptin and insulin deficit and activated by negative energy balance and ghrelin.

POMC and AgRP neuron projections both converge on MC4R neurons in the PVH, which anorexigenic melanocortin peptides activate to suppress food intake and enhance energy expenditure, and orexigenic AgRP neuropeptides inhibit to increase food intake [141; 277]. Also, circulating ghrelin binds its receptor on AgRP neurons, which then release NPY [3].

Negative energy balance and prolonged caloric restriction activate AgRP neurons in part by reducing plasma levels of leptin and insulin that inhibit AgRP neurons. Inactivating this inhibitory input activates AgRP neurons and increases the drive to eat, which promotes positive energy balance and recovery of lost weight [7].

Circulating levels of leptin, insulin, and other hormones serve the hypothalamus with feedback about the availability of energy. When circulating levels of these energy signals decrease during prolonged caloric deficit, increased AgRP neuron excitation recapitulates many behaviors and physiological effects associated with starvation, such as enhanced rewarding properties of food, as well as stimulating food intake [277]. Disruption of this fine-tuned control in the arcuate circuitry leads to dysregulation of energy balance and metabolism [8; 266].

Hypothalamic Regulation of Adiposity and Energy Expenditure

White adipose tissue, the dominant body fat, is comprised of fat cells (adipocytes), stores energy in the form of triglycerides, and can increase fat reserves (lipogenesis) or utilize fat as energy (lipolysis) [278]. Melanocortin signaling regulates lipid metabolism and adiposity via the sympathetic nervous system (SNS) activity; disruption promotes lipid uptake, triglyceride synthesis, and fat accumulation in white adipose tissue [150; 275].

The SNS innervates white adipose tissue, and sympathetic terminals are adjacent to more than 90% of adipocytes. The brain releases norepinephrine from sympathetic terminals, which activate α- and β-adrenergic receptors on adipocytes. This sympathetic outflow is the principal initiator of lipolysis, mediated in part by MC3/4R activity on sympathetic cholinergic neurons [271; 276].

A common frustration for individuals trying to lose weight is the marked compensatory reduction in energy expenditure associated with caloric restriction [277]. AgRP neurons, activated by negative energy balance, shift metabolism toward energy conservation by promoting lipid storage and adipogeneses, elevating carbohydrate fuel use, reducing lipolysis, and thus decreasing energy expenditure in adipose tissue, in part, by suppressing sympathetic outflow to white adipose tissue. NPY release increases food intake and decreases energy expenditure via NPY1R-mediated reduction in downstream sympathetic output to adipose tissue [268]. SNS neurons also produce NPY, which induces vasoconstriction and fat tissue expansion [150].

A key point is that through extensive bidirectional communication, adipose tissue importantly influences energy balance, while CNS and hypothalamus play an essential role in controlling systemic metabolism [279].

Hypothalamic POMC Neurons and Cannabinoids

Cannabis use represents a "wildcard" in appetite mediation by the melanocortin system. By activation of cannabinoid receptor 1 (CB1R), cannabis-induced eating is a hallmark of cannabis use [280].

POMC neurons also produce β-endorphin, an opioid peptide that binds the μ-opioid receptor (MOR). CB1R activation selectively increases β-endorphin, but not α-MSH, release by POMC neurons. Beta-endorphin inhibits AgRP neuron activity, and acute CB1R-induced eating is blocked by naloxone, a MOR antagonist [280].

Thus, cannabis stimulates a switch from α-MSH to β-endorphin release by POMC neurons and subsequently increases appetite and food intake (i.e., "the munchies"). This interesting and paradoxical finding argues against an exclusively anorexigenic role of POMC neurons [266].

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*

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].

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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#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.

Additional Approval: AACN Synergy CERP Category A, CCMC

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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.

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.

Additional Approval: AACN Synergy CERP Category A, CCMC

WOMEN AND CORONARY HEART DISEASE
UPDATE

#33224 • 15 ANCC / 5 Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to identify the unique challenges that face women with heart disease, including prevention, diagnosis, and treatment.

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.

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.

Additional Approval: AACN Synergy CERP Category B, CCMC

HYPERLIPIDEMIAS AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE
UPDATE

#90844 • 10 ANCC / 7 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide a review of hyperlipidemia in the pathogenesis of cardiovascular disease, as well as the therapeutic benefits of pharmacologic and nonpharmacologic approaches to treatment. The objectives are to promote team-based care, foster patient awareness and shared provider-patient decision-making, and promote implementation of lifestyle changes and compliance with guideline-directed therapy for prevention of cardiovascular disease.

Additional Approval: AACN Synergy CERP Category A, CCMC

METABOLIC SYNDROME: A GROWING EPIDEMIC
UPDATE

#91544 • 5 ANCC / 1 Pharm Hour

Book By Mail – $38 • ONLINE – $30

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

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.

Additional Approval: AACN Synergy CERP Category B

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

Course Availability List *(Cont'd)*

LOW BACK PAIN

#94102 • 15 ANCC / 10 Pharm Hours

UPDATE

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.

Additional Approval: AACN Synergy CERP Category A, CCMC

AUTOIMMUNE DISEASES

#94454 • 15 ANCC / 10 Pharm Hours

UPDATE

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.

Additional Approval: AACN Synergy CERP Category A, CCMC

PNEUMONIA

#94673 • 10 ANCC / 5 Pharm Hours

New Guidelines

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.

Additional Approval: AACN Synergy CERP Category A, CCMC

MANAGING DRUG INTERACTIONS WITH DIRECT ORAL ANTICOAGULANTS

#95010 • 1 ANCC / 1 Pharm Hour

NEW!

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.

Additional Approval: AACN Synergy CERP Category A

HUMAN TRAFFICKING AND EXPLOITATION

#96313 • 5 ANCC Hours

MANDATE

Book By Mail – $38 • ONLINE – $30

Purpose: As human trafficking becomes an increasingly more common problem in the United States, healthcare and mental health professionals will require knowledge of human trafficking patterns, the health and mental health needs of human trafficking victims, and successful interventions for victims. The purpose of this course is to increase the level of awareness and knowledge about human trafficking and exploitation so health and mental health professionals can identify and intervene in cases of exploitation.

Additional Approval: AACN Synergy CERP Category B, CCMC

Special Approval: This course meets the Michigan requirement for training in identifying victims of human trafficking.

ANXIETY DISORDERS IN OLDER ADULTS

#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.

Additional Approval: AACN Synergy CERP Category A

IMPLICIT BIAS: THE MICHIGAN REQUIREMENT

#97440 • 2 ANCC Hours

MANDATE

ONLINE ONLY – $30

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

Additional Approval: AACN Synergy CERP Category B

Special Approval: This course meets the Michigan requirement for 2 hours of implicit bias training.

CANNABINOID OVERVIEW

#98010 • 3 ANCC / 3 Pharm Hours

NEW!

Book By Mail – $26 • ONLINE – $18

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the various cannabinoids.

Additional Approval: AACN Synergy CERP Category A

COMMONLY ABUSED SUPPLEMENTS

#98020 • 2 ANCC Hours

NEW!

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the commonly abused supplements and their adverse effects.

Additional Approval: AACN Synergy CERP Category A

NATURAL PSYCHEDELICS

#98320 • 3 ANCC / 3 Pharm Hours

NEW!

Book By Mail – $26 • ONLINE – $18

Purpose: The purpose of this course is to provide healthcare professionals with an increased understanding of natural psychedelics and the considerations associated with the safety, effectiveness, and legal use of these substances.

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.

Additional Approval: AACN Synergy CERP Category A, CCMC

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☐	94280	Pharmacologic and Medical Advances in Obesity Management / 15 Contact Hours	$90

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☐	32014	Childhood Obesity: Impact on Health Care / 5	$38
☐	33224	Women and Coronary Heart Disease / 15	$98
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☐	90844	Hyperlipidemias and Cardiovascular Disease / 10	$68
☐	91544	Metabolic Syndrome: A Growing Disease / 5	$38
☐	93010	Maternal Health Disparities / 4	$32
☐	94102	Low Back Pain / 15	$98
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1. Was the course content new or review?
2. How much time did you spend on this activity?
3. Would you recommend this course to your peers?
4. Did the course content support the stated course objective?
5. Did the course content demonstrate the author's knowledge of the subject?
6. Was the course content free of bias?
7. Before completing the course, did you identify the necessity for education on the topic to improve your nursing practice?
8. Have you achieved all of the stated learning objectives of this course?
9. Has what you think or feel about this topic changed?
10. Did study questions throughout the course promote recall of learning objectives?
11. Did evidence-based practice recommendations assist in determining the validity or relevance of the information?
12. Are you more confident in your ability to provide nursing care after completing this course?
13. Do you plan to make changes in your nursing practice as a result of this course content?

#90120 Pulmonary Embolism 2 Contact Hours	**#95300** Substance Use Disorders 8 Contact Hours	**#94280** Obesity Management 15 Contact Hours
1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review
2. ____ Hours	2. ____ Hours	2. ____ Hours
3. ☐ Yes ☐ No	3. ☐ Yes ☐ No	3. ☐ Yes ☐ No
4. ☐ Yes ☐ No	4. ☐ Yes ☐ No	4. ☐ Yes ☐ No
5. ☐ Yes ☐ No	5. ☐ Yes ☐ No	5. ☐ Yes ☐ No
6. ☐ Yes ☐ No	6. ☐ Yes ☐ No	6. ☐ Yes ☐ No
7. ☐ Yes ☐ No	7. ☐ Yes ☐ No	7. ☐ Yes ☐ No
8. ☐ Yes ☐ No	8. ☐ Yes ☐ No	8. ☐ Yes ☐ No
9. ☐ Yes ☐ No	9. ☐ Yes ☐ No	9. ☐ Yes ☐ No
10. ☐ Yes ☐ No	10. ☐ Yes ☐ No	10. ☐ Yes ☐ No
11. ☒ N/A	11. ☒ N/A	11. ☒ N/A
12. ☐ Yes ☐ No	12. ☐ Yes ☐ No	12. ☐ Yes ☐ No
13. ☐ Yes ☐ No	13. ☐ Yes ☐ No	13. ☐ Yes ☐ No

#90120 Pulmonary Embolism — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____
_____
_____

#95300 Substance Use Disorders and Pain Management — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____
_____
_____

#94280 Pharmacologic and Medical Advances in Obesity Management — 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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May we contact you later regarding your comments about these activities? ☐ Yes ☐ No

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