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# 2024–2025 CME FOR OHIO PHYSICIANS AND PHYSICIAN ASSISTANTS

## INSIDE THIS EDITION

**Substance Use Disorders and Pain Management: MATE Act Training***

**Psychedelic Medicine**

**Pharmacologic and Medical Advances in Obesity Management**

**Includes 15 Pharmacology Hours for Physician Assistants**

We report for ABIM, ABS, ABA, ABP, ABPath, and ABTS, and to CE Broker.

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CME FOR
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# *Substance Use Disorders and Pain Management: MATE Act Training*

**Have you already completed MATE Act Training? You can still use this course to meet your state and MOC CME requirements!**

***Special Approvals***

This course meets the requirements for up to 8 hours of opioid/controlled substance/pain management/addiction education for the following states: AL, AK, AZ, AR, CA, CT, DE, GA, ID, IL, IN, IA, KS, KY, LA, MA, MD, ME, MI, MN, MS, NC, NE, NH, NJ, NM, NV, NY, RI, SC, TX, VA, VT, WA, WI, and WY.

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***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.

### *Division Planner*

John M. Leonard, MD

### *Senior Director of Development and Academic Affairs*

Sarah Campbell

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## INTRODUCTION

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

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

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

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

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

## SUBSTANCE USE DISORDER SCREENING AND DIAGNOSIS

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

## RISK FACTORS

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

### Genetic Predisposition

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

### Children with Conduct Problems

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

### Stress and Distress

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

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

### Other Mental Disorders

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

### Environmental Stimuli

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

## SCREENING

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

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

  

| 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* |

**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.


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

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

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

**Strength of Recommendation**: Strong for

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

#### Contingency Management

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

  

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

**Community Reinforcement**

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

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

**Motivational Interventions**

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

**Coping and Social Skill Training**

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

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

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

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

**Drug Counseling**

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

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

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

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

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

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

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

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

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

## 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<br>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<br>IM: 380 mg/week | PO: 25 mg/day<br>IM: 380 mg/week | Injection site reactions, anxiety, syncope | PO, IM | Not scheduled |
| Buprenorphine (Belbuca, Buprenex, Butrans, Probuphine, Sublocade) | SQ: 100–300 mg/ month<br>SL: 2–24 mg/day | SQ: 300 mg/month<br>Implant: 4 implants<br>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<br>IM: 380 mg/month | PO: 50 mg/day<br>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<br>Inhaler: 6–16 cartridges/day<br>Lozenge: Titrate to 1 lozenge every 4 to 8 hours<br>Nasal spray: Maximum 80 sprays/day<br>Patch: One patch/day for 8 weeks | Gum: 1 to 2 pieces/ hour (2 mg/piece)<br>Inhaler: 6 cartridges/ day<br>Lozenge: One lozenge every 1 to 2 hours<br>Nasal spray: 1 spray in each nostril once or twice per hour<br>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*

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].

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

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

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

### *Harm Reduction*

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

### *Detoxification*

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

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

However, some withdrawal symptoms, including anxiety and myalgias, are resistant to clonidine; benzodiazepines and 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].

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

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

**Strength of Recommendation:** Strong for

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

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

  

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


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

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

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

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

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

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

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

### Tobacco Use Disorder

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

#### *Bupropion*

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

#### *Varenicline Tartrate*

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

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

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

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

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

## FACTORS IMPACTING RECOVERY

**Stigma**

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

**Trauma**

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

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

**Social Determinants of Health**

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

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

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

### LEGAL AND ETHICAL ISSUES IN THE TREATMENT OF SUBSTANCE USE DISORDERS

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

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

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

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

## PAIN MANAGEMENT AND SUBSTANCE MISUSE

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

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

### PAIN MANAGEMENT APPROACHES

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

The Centers for Disease Control and Prevention (CDC) originally published *Guideline for Prescribing Opioids for Chronic Pain—United States, 2016* in an effort to address an ongoing crisis of prescription opioid misuse, abuse, and overdose [125]. While these guidelines were based on the best available evidence at the time, there was some criticism that they were too focused on limiting opioid prescriptions—to the point of patients and prescribers complaining of stigma and reduced access to needed opioid analgesics. In response to this and to the availability of new evidence, the CDC published updates

  

to the guideline in 2022 [127]. The updated clinical practice guideline is intended to achieve improved communication between clinicians and patients about the risks and benefits of pain treatment, including opioid therapy for pain; improved safety and effectiveness for pain treatment, resulting in improved function and quality of life for patients experiencing pain; and a reduction in the risks associated with long-term opioid therapy, including opioid use disorder, overdose, and death [127].

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

**Acute Pain**

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

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

**Chronic Pain**

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

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

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

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

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

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

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

**Palliative Care and Pain at the End of Life**

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

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

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

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

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

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

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

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

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

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

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

## CREATING A TREATMENT PLAN AND ASSESSMENT OF ADDICTION RISK

Information obtained by patient history, physical examination, and interview, from family members, a spouse, or state prescription drug monitoring program (PDMP), and from the use of screening and assessment tools can help the clinician to stratify the patient according to level of risk for developing problematic opioid behavioral responses (***Table 3***) [143; 144].

  

| 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* |

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].

***Screening Instrument or Substance Abuse Potential (SISAP)***

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

***CAGE and CAGE-AID***

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

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

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

**Considerations for Pain Management in Patients with Comorbid Opioid Use Disorder**

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

  

consultation with their opioid treatment program [150]. The *ASAM National Practice Guideline for the Treatment of Opioid Use Disorder (2020 Focused Update)* provides additional recommendations for the management of patients receiving medications for opioid use disorder who have planned surgeries for which nonopioid therapies are not anticipated to provide sufficient pain relief [150].

**Informed Consent and Treatment Agreements**

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

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

**Periodic Review and Monitoring**

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

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

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

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

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

***Involvement of Family***

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

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

| 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*

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

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

  

**Concurrent Use of Benzodiazepines**

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

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

**Consultation and Referral**

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

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

**Medical Records**

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

**Patient Education on the Use and Disposal of Opioids**

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

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

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

There are no universal recommendations for the proper disposal of unused opioids, and patients are rarely advised of what to do with unused or expired medications [161]. According to the FDA, most medications that are no longer necessary or have expired should be removed from their containers, mixed with undesirable substances (e.g., cat litter, used coffee grounds), and put into an impermeable, nondescript container (e.g., disposable container with a lid or a sealed bag) before throwing in the trash [162]. Any personal information should be obscured or destroyed. The FDA recommends that certain medications, including oxycodone/acetaminophen (Percocet), oxycodone (OxyContin tablets), and transdermal fentanyl (Duragesic Transdermal System), be flushed down the toilet instead of thrown in the trash [162; 163]. The FDA provides a

free toolkit of materials (e.g., social media images, fact sheets, posters) to raise awareness of the serious dangers of keeping unused opioid pain medicines in the home and with information about safe disposal of these medicines. The Remove the Risk Outreach toolkit is updated regularly and can be found at https://www.fda.gov/drugs/ensuring-safe-use-medicine/safe-opioid-disposal-remove-risk-outreach-toolkit [163]. Patients should be advised to flush prescription drugs down the toilet only if the label or accompanying patient information specifically instructs doing so.

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

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

**Discontinuing Opioid Therapy**

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

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

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

**Considerations for Non-English-Proficient Patients**

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

## IDENTIFICATION OF DRUG DIVERSION/SEEKING BEHAVIORS

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

  

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

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

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

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

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

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

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

**Level of Evidence**: Expert Opinion/Consensus Statement

## INTERVENTIONS FOR SUSPECTED OR KNOWN ADDICTION OR DRUG DIVERSION

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

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

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

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

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

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

### COMPLIANCE WITH STATE AND FEDERAL LAWS

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

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

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

#### Controlled Substances Laws/Rules

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

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

#### State-Specific Laws and Rules

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

## CONCLUSION

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

**Customer Information/Answer Sheet/Evaluation insert located between pages 56–57.**

  

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

*This is an open book test. Please record your responses on the Answer Sheet.*
*A passing grade of at least 70% must be achieved in order to receive credit for this course.*

*In accordance with the AMA PRA Category 1 Credit™ system,*
*physicians must complete and pass a post-test to receive credit.*

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

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

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

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

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

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

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

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

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

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

*Test questions continue on next page* ➞

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

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

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

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

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

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

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

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

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

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

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

Be sure to transfer your answers to the Answer Sheet insert located between pages 56–57.

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

  

# Psychedelic Medicine and Interventional Psychiatry

**In addition to receiving *AMA PRA Category 1 Credit™*, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board: 10 ABIM MOC Points, 10 ABS MOC Points, 10 ABP Points.**

### *Audience*

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

### *Course Objective*

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

### *Learning Objectives*

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

1. Outline factors that have contributed to the rise in interest in psychedelic and interventional psychiatry.
2. Define terms related to the discussion of psychedelic and interventional psychiatry.
3. Discuss the history of psychedelics in medical care.
4. Evaluate factors that may impact the provision of psychedelic or interventional psychiatry techniques, including stigma, setting, and culture.
5. Outline the role of psilocybin and ketamine in psychiatric care.
6. Describe how MDMA and ibogaine may impact mental health.
7. Review the clinical effects of kratom, LSD, and mescaline.
8. Discuss the potential clinical role of nitrous oxide, ayahuasca, and dimethyltryptamine (DMT).
9. Describe how psychedelics may be incorporated into the treatment of mental health disorders, including treatment-resistant depression, post-traumatic stress disorder, and substance use disorders.
10. Identify interventional approaches that may be used in the treatment of mental health disorders.

### *Faculty*

**Mark S. Gold, MD, DFASAM, DLFAPA**, is a teacher of the year, translational researcher, author, mentor, and inventor best known for his work on the brain systems underlying the effects of opiate drugs, cocaine, and food. Dr. Gold was a Professor, Eminent Scholar, Distinguished Professor, Distinguished Alumni Professor, Chairman, and Emeritus Eminent Scholar during his 25 years at the University of Florida. He was a Founding Director of the McKnight Brain Institute and a pioneering neuroscience-addiction researcher funded by the NIH-NIDA-Pharma, whose work helped to de-stigmatize addictions and mainstream addiction education and treatment. He also developed and taught courses and training programs at the University of Florida for undergraduates and medical students. (A complete biography appears at the end of this course.)

### *Faculty Disclosure*

Contributing faculty, Mark S. Gold, MD, DFASAM, DLFAPA, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

### *Division Planner*

John M. Leonard, MD

### *Senior Director of Development and Academic Affairs*

Sarah Campbell

### *Division Planner/Director Disclosure*

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 10 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

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

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 10 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

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

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

## INTRODUCTION

A new and intense interest in psychedelic drugs and interventional medicine is occurring now in the United States and worldwide, as scientists are exploring and discovering innovative ways to treat challenging psychiatric problems, including treatment-resistant depression, suicidal major depressive disorder, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and substance use disorders, as well as multiple other psychiatric problems that have largely been impervious to traditional treatment. Psychedelic medicine refers to the use of drugs that are hallucinogenic and/or anesthetic and that have a unique action on the brain. These approaches may be used only in research situations or may be in current and active use as treatments. In contrast, interventional psychiatry refers to the use of brain-stimulating therapies to treat severe psychiatric disorders. These therapies include electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS). As with psychedelic medicine, interventional medicine may be used to provide relief for patients with multiple major and previously unremitting severe psychiatric disorders, although there is still much to learn about these therapies. This course will provide an overview of both of these forms of treatment, with an emphasis on psychedelic medicine.

Today, psychedelics like *N*, *N*-dimethyltryptamine (DMT), psilocybin, 3,4-methylenedioxymethamphetamine (MDMA), and lysergic acid diethylamide (LSD) are being explored to treat various psychiatric disorders. Trials of these drugs are in different stages, and the timeline for U.S. Food and Drug Administration (FDA) approval is not always obvious. While ketamine was approved in 2020, most experts believe the first psychedelic approval will come in 2024, likely for PTSD rather than treatment-resistant depression, even though treatment with psilocybin was found to relieve symptoms of major depressive disorder for at least one year for some patients in a 2022 Johns Hopkins study [1]. The safety and efficacy of MDMA-assisted therapy is currently under Phase 3 investigation, but concerns remain regarding efficacy and potential adverse effects. As of 2022, the Multidisciplinary Association of Psychedelic Studies (MAPS) is sponsoring MAPP2, the second of two Phase 3 trials to support FDA approval of MDMA as a breakthrough-designated therapy for the estimated 9 million adults in the United States who experience PTSD each year. In MAPS's first Phase 3 study, 88% of participants with severe PTSD experienced a clinically significant reduction in PTSD diagnostic scores two months after their third session of MDMA-assisted therapy, compared with 60% of placebo participants. Additionally, 67% of participants in the MDMA group no longer met the criteria for PTSD two months after the sessions, compared with 32% of participants in the placebo group [2].

When effective, psychedelic medicine is analogous to a "resetting" of the brain. It is somewhat like when a computer runs awry, and nothing of many actions that the user tries improves the situation. In frustration, the user shuts off the machine, but when the device is turned back on, everything works perfectly. The machine has reset itself. Similarly, psychedelic drugs, when effective, may aid the brain in a sort of resetting. Depending on the individual and the drug, the person may find they have marked improvements in symptoms of depression, PTSD, addiction, or other severe psychiatric problem.

As a result of today's research renaissance on psychedelic drugs, there is a new era of hope for people with major psychiatric disorders who have been largely unresponsive to traditional treatments.

One concern about psychedelic medicine is that many of the drugs may induce hallucinations, even in the low doses used for depression. Mental health professionals who prescribe or administer the drugs will need to ensure patients are monitored adequately. In some cases, the person receiving the drug is hospitalized, but in others, the drug is administered and changes observed in an office setting.

Ketamine's efficacy and protocols to ensure safety have resulted in thousands of patients being treated and reporting excellent responses for treatment-resistant depression. However, the ideal drug would provide the benefits without the hallucinatory side effects. In one unique experiment with mice, researchers effectively blocked 5-HT2A, the serotonin-detecting receptor, and this action appeared to stop mice being administered psilocybin from hallucinating ("tripping"). The antidepressant effects were unaltered in this study, as evidenced by the mice resuming consumption of sugar water, an act they had abandoned while depressed [5]. This is an area of great interest, with the potential that the hallucinations induced by psychedelic drugs could be blocked and increase the acceptability of these agents in the general treatment of depression.

Of course, there are many who believe that the psychedelic trip itself, hallucinations and all, is the crucial experience that allows people to experience psychic relief. These individuals believe that eliminating the crucial experience of hallucination would essentially block the full efficacy of the drug. This issue is likely to continue to be discussed and debated as the science advances.

Psychedelic drugs are often divided into two categories: classic and non-classic or dissociative. The classic psychedelics are usually derived from naturally occurring compounds and include such drugs as psilocybin, LSD, and DMT, an active component of ayahuasca, an increasingly popular sacramental drink originating from South America. The dissociative psychedelics are typically newer analogs and include ketamine, phencyclidine (PCP), MDMA, mescaline, *Salvia divinorum*, and dextromethorphan (DXM). While considered drugs of abuse, most agents being tested in psychedelic medicine clinical trials

are not self-administered by laboratory animals, the usual test for abuse and dependence liability. If anything, hallucinogens tend to lose their ability to produce changes in the person over time and with regular use. These drugs are all variations on tryptamine, and while they may increase dopamine, they tend to do this through an indirect mechanism.

In their 1979 publication, Grinspoon, Grinspoon, and Bakalar define a classic psychedelic drug as [6]:

> A drug which, without causing physical addiction, craving, major physiological disturbances, delirium, disorientation, or amnesia, more or less reliably produces thought, mood, and perceptual changes otherwise rarely experienced except in dreams, contemplative and religious exaltation, flashes of vivid involuntary memory, and acute psychosis.

While the classic versus non-classic designation is of interest to researchers, it is likely not an important distinction for prescribers or patients.

## THE IMPORTANCE OF PSYCHEDELIC AND INTERVENTIONAL MEDICINE

There are multiple reasons health and mental health professionals would benefit from education about both psychedelic and interventional medicine. Psychedelic medicine is a multi-billion-dollar industry and is rapidly growing. It is likely that many healthcare professionals will become involved with these approaches as they enter more widespread use.

Many people in the United States suffer from severe depression, and suicide is a public health problem. In 2020, 21,570 people in the United States died from homicide, a significant increase from the number just one year earlier [7]. However, it did not come close to the suicide rate. In 2020, 45,855 people in the United States died from suicide. The annual U.S. suicide rate increased 30% between 2000 and 2020 [7]. As such, depression and suicide are major health problems in the United States today, and approaches to reverse depression rapidly and safely are greatly needed.

It is also important to consider the frustration of many patients with treatment-resistant depression and other disorders, many of whom have turned to cannabis to obtain relief. The majority of states have enacted laws approving medical marijuana, although its efficacy in the treatment of PTSD, depression, and other psychiatric disorders is often lacking [8]. Patients are clearly open to seeking help wherever it may be, whether evidence and healthcare professionals support the approaches. As such, it is vital that clinicians be aware of and knowledgeable regarding novel uses of psychedelic drugs and interventional psychiatry to best serve their patients.

Academic experts, universities, and medical groups continue to research psychedelic medicine, with exciting major breakthroughs in the treatment of depression/anxiety at the end of life and providing relief to patients with treatment-resistant depression, PTSD, and other disorders that most psychiatrists consider difficult to treat. This research will be detailed later in this course.

### TREATMENT-RESISTANT DEPRESSION AND THE RISK OF SUICIDE

As noted, the suicide rate in the United States is more than twice as high as the homicide rate [7]. In 2019, suicide was the second leading cause of death for people 10 to 34 years of age and the tenth leading cause of death across all age groups (***Table 1***). Overall, suicide accounts for 1.7% of all deaths in the United States. Although official national statistics are not compiled on attempted suicide (i.e., nonfatal actions), it is estimated that 1.2 million adults (18 years of age and older) attempted suicide in 2020 [9]. Overall, there are roughly 25 attempts for every death by suicide; this ratio changes to 100 to 200:1 for the young and 4:1 for the elderly [9].

People with depression may experience suicidal ideation and behaviors, which can subsequently lead to suicide completions. As illustrated by ***Figure 1***, in 2020, adults 18 to 25 years of age had the highest risk for a major depressive episode, followed by those 25 to 49 years of age. In addition, individuals of two or more races had the highest risk for depression (15.9%), followed by White individuals (9.5%).

Suicidal behaviors are a major problem in the United States, as depicted in the converging circles shown in ***Figure 2***. This figure demonstrates that 12.2 million adults seriously considered suicide in 2020, represented by the outer circle, while 3.2 million adults made suicide plans, and 1.2 million adults attempted suicide. Of those adults who attempted suicide in 2020, 920,000 had made a suicide plan; 285,000 adults had made no such plan prior to the attempt [10; 12].

Clearly, action is needed to help address depression and suicide in the United States, and psychedelic and interventional medicine may have a role.

### POOR RESPONSE TO ANTIDEPRESSANTS

When they were first introduced, the monoamine oxide (MAO) inhibitors and tricyclic antidepressants were perceived as wonder drugs for depression. However, MAO inhibitors require strict dietary constraints, and both drug classes are associated with multiple troubling side effects. In contrast, when selective serotonin reuptake inhibitors (SSRIs) were introduced, they were much easier to prescribe and expanded treatment approaches to include primary care. Unfortunately, for many patients, SSRIs did not help as much as expected—or indeed at all, in some cases. Today, it is clear that non- or under-response to pharmacotherapy for major depression is far more common than was realized at the time. For example, researchers have

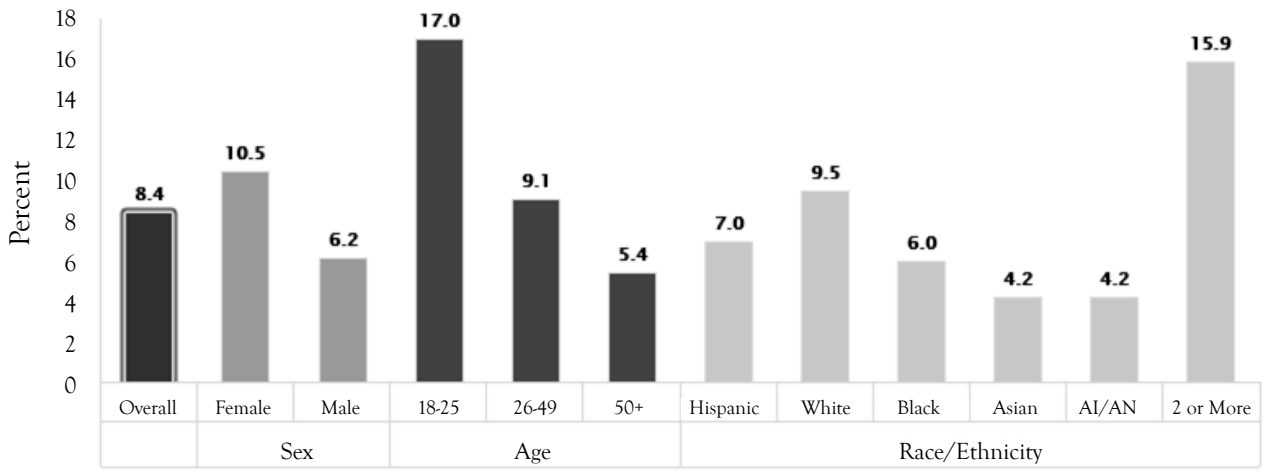
| LEADING CAUSE OF DEATH IN THE UNITED STATES FOR SELECT AGE GROUPS, 2019 | | | | | | | |
|---|---|---|---|---|---|---|---|
| Rank | Age (in Years) | | | | | | |
| | 10–14 | 15–24 | 25–34 | 35–44 | 45–54 | 55–64 | All Ages |
| 1 | Unintentional injury (778) | Unintentional injury (11,755) | Unintentional injury (24,516) | Unintentional injury (24,070) | Malignant neoplasms (35,587) | Malignant neoplasms (111,765) | Heart disease (659,041) |
| 2 | Suicide (534) | Suicide (5,954) | Suicide (8,059) | Malignant neoplasms (10,695) | Heart disease (31,138) | Heart disease (80,837) | Malignant neoplasms (599,601) |
| 3 | Malignant neoplasms (404) | Homicide (4,774) | Homicide (5,341) | Heart disease (10,499) | Unintentional injury (23,359) | Unintentional injury (24,892) | Unintentional injury (173,040) |
| 4 | Homicide (191) | Malignant neoplasms (1,388) | Malignant neoplasms (3,577) | Suicide (7,525) | Liver disease (8,098) | CLRD (18,743) | CLRD (156,979) |
| 5 | Congenital anomalies (189) | Heart disease (872) | Heart disease (3,495) | Homicide (3,446) | Suicide (8,012) | Diabetes (15,508) | Stroke (150,005) |
| 6 | Heart disease (87) | Congenital anomalies (390) | Liver disease (1,112) | Liver disease (3,417) | Diabetes (6,348) | Liver disease (14,385) | Alzheimer disease (121,499) |
| 7 | CLRD (81) | Diabetes (248) | Diabetes (887) | Diabetes (2,228) | Stroke (5,153) | Stroke (12,931) | Diabetes (87,647) |
| 8 | Influenza/ pneumonia (71) | Influenza/ pneumonia (175) | Stroke (585) | Stroke (1,741) | CLRD (3,592) | Suicide (8,238) | Nephritis (51,565) |
| 9 | Stroke (48) | CLRD (168) | Complicated pregnancy (532) | Influenza/ pneumonia (951) | Nephritis (2,269) | Nephritis (5,857) | Influenza/ pneumonia (49,783) |
| 10 | Benign neoplasms (35) | Stroke (158) | HIV (486) | Septicemia (812) | Septicemia (2,176) | Septicemia (5,672) | Suicide (47,511) |
| CLRD = chronic lower respiratory disease, HIV = human immunodeficiency disease. | | | | | | | |
| *Source: [10]* | | | | | | | *Table 1* |

found that antidepressants are ineffective for at least one-third of individuals who take them [2]. Suboptimal responses are also common. Many patients for whom the drugs do not work will recalibrate their expectations and accept the treatment response as the best they can hope to achieve. Treatment discontinuation is common among frustrated patients.

It is also important to note that even when antidepressants actually are efficacious, it usually takes at least three or four weeks for the drug to begin to take effect. Tricyclic antidepressants, MAO inhibitors, SSRIs, and serotonin and norepinephrine reuptake inhibitors (SNRIs) all share this issue of a delayed onset of action. Psychiatrists and neuroscientists have been unable to develop faster-acting medications for depression to date. This means that many people with severe depression could take an antidepressant very faithfully for weeks without any relief. These patients may give up hope and halt treatment or try again with another antidepressant or medication combination.

As with any pharmacotherapy, antidepressants have many possible adverse effects, including weight gain, anorgasmia, sluggishness, anxiety, insomnia, and suicidal ideation. As such, a patient may experience no improvements in depression symptoms while also developing adverse drug effects. This is not the end of consequences; discontinuation symptoms are also a concern. Antidepressant discontinuation symptoms can be very challenging. For example, abruptly ending fluoxetine

**PAST YEAR PREVALENCE OF MAJOR DEPRESSIVE EPISODE AMONG U.S. ADULTS, 2020**

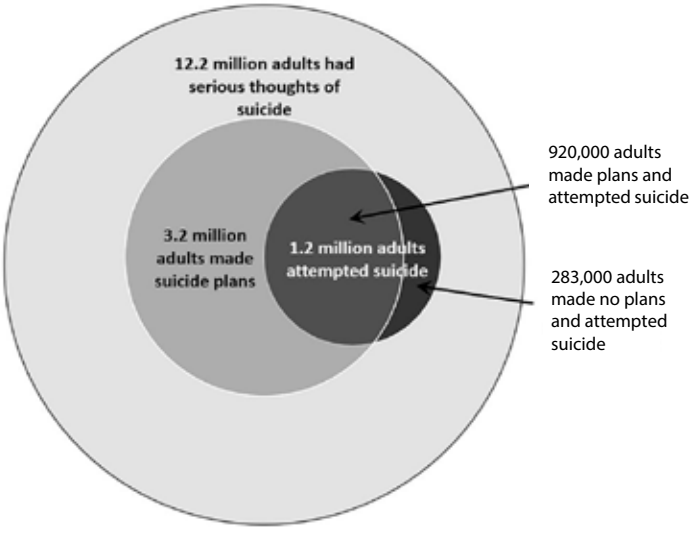



AI/AN = American Indian/Alaska Native

*Source: [11]*

*Figure 1*

**SUICIDAL BEHAVIORS IN THE UNITED STATES, 2020**




*Source: [10; 12; 14]*

*Figure 2*

can cause nightmares, vomiting, and irritability. In most cases, patients who no longer wish to take an antidepressant should taper off the drug on a defined schedule [3].

To recap, patients may take antidepressants for months without significant improvements in depression symptoms while also experiencing side effects, and when they stop taking these ineffective drugs, they suffer more side effects unless they carefully taper off. In contrast, some psychedelic drugs have the potential to provide relief in a few sessions, with lasting efficacy over months or even years, although further research is needed. This contrast is the main reason that so many mental health professionals and patients are intrigued about the possibilities of psychedelic medicine, particularly for more difficult cases.

It is not clear why antidepressants work for some patients and not for others. Some have hypothesized it may be related to the size and shape of a person's neurons, which can vary considerably [3]. Another possible contributing factor is the similar mechanisms of action among the different classes of antidepressants. These agents increase blood levels of serotonin, dopamine, or norepinephrine. In contrast, some psychedelic drugs, such as ketamine, are *N*-methyl-D-aspartate (NMDA)/glutamate receptor antagonists. This represents a completely different target for antidepressant mechanism of action and also a novel approach to treating depression.

There is also some evidence that ketamine can reverse suicidality or depression after a single dose, which suggests that the drug reverses a neurochemical deficit that is close to the problem. Ketamine and psychedelic drugs are effective at promoting plasticity, reconnections, and healing within the brain, a feat beyond the capabilities of traditional antidepressants or most other drugs. Researchers have found that neuroplastic changes, specifically atrophy of neurons in the prefrontal cortex, are an underlying etiology of depression and other mood disorders. The extent to which these drugs, and ketamine in particular, are able to promote structural and functional plasticity in the prefrontal cortex is believed to underlie the fast-acting antidepressant properties [4]. Other drugs, such as LSD and DMT, may stimulate the formulation of synapses [4]. Psychedelic drugs may also create new connections within the brain, although much more research is needed to understand how and why these drugs may be effective in treating serious psychiatric disorders in some who have heretofore not proven responsive to traditionally effective treatments.

## A GROWING MARKET

Certainly, psychedelic medicine is regarded as a major and burgeoning healthcare market. Data Bridge Market Research has estimated that the market for psychedelic drugs will more than triple, from about $2 billion in 2019 to nearly $7 billion by 2027 [13]. Other estimates are even more favorable; a report from Research and Markets anticipates a market of $10.75 billion in psychedelic drugs by 2027 [13]. In a post-COVID world in which the numbers of people with reported depression have increased by as much as three times, potentially effective treatment options should not be ignored.

It has been estimated that at least 50,000 therapists will be needed by 2031 to provide psychedelic-assisted therapy to patients, and as a result, some organizations have already begun to increase their hiring. The key types of therapies used will be cognitive-behavioral therapy (CBT), acceptance and commitment therapy (ACT), or other types of therapy adapted to psychedelic treatment [15].

The current high interest in psychedelic medicine may stimulate pharmaceutical companies to research and develop novel drug treatments for major psychiatric problems beyond the traditional classes of drugs that solely target serotonin, norepinephrine, and dopamine, which would be yet another positive consequence.

## CONSUMER INTEREST

At the same time that the federal government has somewhat loosened its tight reins on psychedelic medicine and researchers and medical professionals have begun to explore the use of these agents, there has been a dramatic increase in interest among consumers in Schedule I drugs, particularly in cannabis, but also in psilocybin and other psychedelic drugs. As of 2022, 37 states as well as the District of Columbia and four U.S. territories allow the medical use of cannabis ("medical marijuana") [16]. (Note that medical use of cannabis is a bit of a misnomer, as prescribers generally have little or no involvement with patients who take the drug and it has not attained FDA approval for any condition.) In addition, the U.S. House of Representatives passed a bill to decriminalize cannabis use in 2022 [17]. In addition, 18 states, the District of Columbia, and 2 U.S. territories have legalized the recreational use of cannabis for adults [18]. This followed several years of decriminalization at the local and state levels. While cannabis is not considered a psychedelic drug, its shift toward decriminalization and medicinal use is a sign that a similar path may be beginning for other Schedule I drugs with potential psychiatric benefit. Further, in states that allow medical or recreational use of cannabis for adults, the federal government has largely backed away from taking any punitive measures against individuals who use the drug, even though cannabis remains illegal at a federal level.

This movement may already be advancing with psychedelic drugs. This began with the decriminalization of psilocybin in Denver, Colorado, in 2019, followed by Oakland and Santa Cruz, California. In 2021, the city of Cambridge, Massachusetts, passed a law decriminalizing all "entheogenic plants," which includes the drugs ayahuasca, ibogaine, and psilocybin [19]. As of 2022, the largest city to decriminalize psilocybin is Seattle, Washington [19]. In 2020, the state of Oregon approved the use of psilocybin by consumers [20]. Also in 2020, the District of Columbia decriminalized the use of psilocybin mushrooms as well as other substances found in peyote and ayahuasca [20]. Other states are considering taking similar actions. In 2021, Health Canada, the premier health agency in Canada, approved trials of MDMA-assisted therapy for the treatment of PTSD [15]. It is important to note that it can be dangerous for psilocybin and other psychedelic drugs to be used by individuals who do not understand its risks. As popularity and interest in the medical use of these agents increases, clinicians have a responsibility to educate themselves and their patients about the safe and appropriate use of psychedelics.

A major factor in the popularity of psychedelic drugs is frustration resulting from unrelenting depression, anxiety, chronic pain, or other health and mental health conditions. Some patients may have already tried cannabis to address these conditions, with varying levels of success.

| PSYCHEDELIC PSYCHIATRY TRAINING PROGRAMS |
|---|
| **Hopkins-Yale-NYU**<br>https://medicine.yale.edu/news-article/grant-supports-development-of-training-for-psychiatrists-in-psychedelic-medicine |
| **MAPS**<br>https://mapspublicbenefit.com/training |
| **Mount Sinai**<br>https://icahn.mssm.edu/research/center-psychedelic-psychotherapy-trauma-research/training-education |
| *Source: Compiled by Author* *Table 2* |

### GROWING BODY OF RESEARCH FROM RESPECTED ACADEMIC AND PHYSICIAN LEADERS

Although researchers have historically chosen to avoid or been blocked from researching psychedelics because of bans by the federal government, this has changed in the past few decades. For example, in 2006, Johns Hopkins Medicine began their research on psychedelic medicine, subsequently producing more than 80 peer-reviewed clinical studies by 2020 [21]. A new home for the Center for Psychedelic and Consciousness Research was created in 2020, the first such establishment in the United States [21]. Private donors provided funding to launch the Center, and since its opening, the Center has also received federal funding for research. In addition, Yale, Massachusetts General Hospital/Harvard, and other psychiatric and research excellence centers are studying psychedelic medications as treatment options for serious psychiatric disorders.

In addition, training programs focusing on psychedelic psychiatry are being established (***Table 2***). Johns Hopkins, New York University, and Yale are collaborating to create a psychedelics-psychiatrist program funded by a grant facilitated by Heffter Research Institute [22].

## DEFINITIONS

Clear definitions of the concepts related to psychedelic drugs and interventional psychiatry are helpful. The following is a glossary of terms used throughout this course.

**Classic psychedelic**: Refers to older hallucinogenic drugs, such as psilocybin and LSD. These agents are often derived from natural sources.

**Deep brain stimulation**: With the use of implanted electrodes, the brain is stimulated to treat such psychiatric problems as treatment-resistant depression.

**Electroconvulsive therapy (ECT)**: Stimulation of the brain causing a seizure. This therapy is administered under sedation and is used to help patients with severe psychiatric diagnoses.

**Hallucinogen**: Drug that may cause the user to experience visual, auditory, or other types of hallucinations.

**Neuromodulation therapy**: The use of noninvasive or invasive means to stimulate the brain in order to treat serious psychiatric problems.

**Psychedelic medicine**: The use of mind-altering (typically but not always hallucinogenic or dissociative) drugs by mental health professionals to improve or even provide remission from severe psychiatric problems, such as depression, PTSD, anxiety, and substance use disorders.

**Set**: Refers to the patient's mindset. For example, a person who is anxious and fearful is less likely to have a positive experience with psychedelic medicine than a person who has an open and positive outlook.

**Setting**: Refers to the overall ambiance in which psychedelic medicine is administered. A pleasant atmosphere that makes the individual feel safe is best.

**Transcranial magnetic stimulation**: A noninvasive form of therapy that uses large magnets external to the patient to stimulate the brain.

**Vagus nerve stimulation**: Invasive stimulation of the vagus nerve in order to treat serious, treatment-resistant psychiatric diagnoses.

## PONDERING PSYCHEDELICS

More than 50 years have passed since the federal Controlled Substances Act first criminalized the use of psychedelics in the United States in 1970. The initial use (and misuse) of psychedelic drugs in that era was primarily associated with Timothy Leary, a Harvard professor who promoted the nonmedical use of LSD, a practice subsequently adopted by the amorphous "hippie" counterculture movement of the 1960s and 1970s. Dr. Leary was famously noted as advising his followers to "turn on, tune in, and drop out," scandalizing much of the conservative population of the time. Numerous events led to Leary's loss of reputation, academic standing, and position, but his impact during this period was indisputable. In response to this movement, drugs such as LSD, DMT, psilocybin, and mescaline were all placed in the Schedule I drugs category under the Controlled Substances Act 1970 (***Table 3***).

| PSYCHEDELIC DRUG SCHEDULING | |
|---|---|
| **Drug** | **Schedule** |
| Ayahuasca/DMT | I |
| Ibogaine | I |
| Ketamine | III |
| Kratom | Not scheduled |
| LSD | I |
| Mescaline | I |
| Nitrous oxide | Not scheduled |
| Psilocybin | I |
| MDMA ("Molly," "Ecstasy") | I |
| *Source: [23]* | *Table 3* |

The categorization of psychedelics as Schedule I drugs immediately halted intense scientific research on psychedelics, which had begun in the 1950s. This prohibition on psychedelic drug research significantly delayed advances in medical knowledge on the therapeutic uses of these agents. While much of the focus at that time was on Timothy Leary and the counterculture's recreational LSD use, some researchers had demonstrated beneficial effects with psychedelic medicine in end-of-life care as well as in the treatment of addiction and other severe psychiatric problems [24].

This research did not restart in the United States in any meaningful way until the 21st century. In this new wave of research, researchers in Phase 2 and 3 clinical trials of psychedelic medications have found the possibility of remission in diverse psychiatric populations (including in patients with PTSD, depression, eating disorders, and substance use disorders) as well as reduction in end-of-life anxiety and despair in those with terminal diagnoses [25]. At the same time, researchers have explored the use of older drugs (e.g., nitrous oxide, ketamine) to treat unrelenting psychiatric disorders.

Another interesting avenue of research has been in the field of addiction medicine. There is some evidence that certain psychedelic drugs, particularly psilocybin, may act as a sort of "anti-gateway drug." Years ago, there was a belief that some (or all) drugs were "gateway drugs," leading inevitably to taking other drugs; for example, this perspective holds that people who smoked marijuana would eventually progress to using "harder" drugs, injecting heroin or other opioids. This theory has largely been discredited and devalued. In fact, several studies have indicated that persons who use hallucinogens are less likely to progress to harder drugs. In one study, researchers used data from nearly 250,000 respondents from the National Survey on Drug Use and Health over the period 2015–2019. Respondents were asked about their past use of classic psychedelics, and these results were then compared to their later abuse (or non-use) of opioids. Individuals who had used psilocybin ("magic mushrooms") in the past had a significantly lower rate (30% lower than average) of opioid misuse and abuse later. This finding was not replicated with other psychedelic drugs [26]. An earlier study using National Survey on Drug Use and Health data for the period 2008–2013 found that past use of classic psychedelics decreased the risk for past-year opioid dependence by 27% and of opioid abuse by 40% [27].

Both of these studies relied on individuals reporting on their past use of psychedelic drugs, and there are multiple possible issues with this type of retrospective reporting. But the idea that past use of drugs such as psilocybin could be protective against opioid misuse and dependence in the future is promising, given the ongoing opioid epidemic in the United States.

## A BRIEF HISTORY OF PSYCHEDELICS

It is unclear how long the various psychedelic substances have been used worldwide, but it is safe to say that some have been used for thousands of years in religious and tribal ceremonies. The earliest known written record of the use of psilocybin mushrooms appeared in the Florentine Codex, a manuscript of ethnographic research of Mesoamerica, particularly of Mexico and the Aztecs, compiled between 1529 and 1579. Psilocybin, mescaline, and ayahuasca (a concoction often brewed in a tea and that includes the psychedelic chemical DMT) have all been used in religious ceremonies in indigenous societies in South and Central America for centuries. The hallucinogenic effects of some plants and fungi also have been known by indigenous cultures and were deliberately exploited by humans for thousands of years. Fungi, particularly some types of mushrooms, are the principal source of naturally occurring psychedelics. Historically, the mushroom extract psilocybin has been used as a psychedelic agent for religious and spiritual ceremonies and as a therapeutic option for neuropsychiatric conditions [28].

### Early Days of LSD

Modern pharmaceutical research on psychedelics started in earnest in 1930s Basel, Switzerland, with research chemist Albert Hofmann. Seeking to create a synthetic alkaloid to the ergot fungus, he developed LSD-25 in 1938. The uses of the drug were not immediately obvious, so it sat on a shelf for five years until Hofmann decided to repeat his synthesis of the chemical. Despite his care, Hofmann accidentally contaminated himself with the drug and thereafter experienced highly unusual sensations as well as dizziness. He described his experience as [29]:

> I lay down and sank into a not unpleasant intoxicated-like condition, characterized by an extremely stimulated imagination. In a dreamlike state, with eyes closed (I found the daylight to be unpleasantly glaring), I perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors. After some two hours, this condition faded away.

Hofmann decided to experiment on himself with what he believed to be a very low dose of LSD, but the dose was high enough for him to experience what he perceived to be demonic possession and other lurid sensations. His physician was called and only noted that Hofmann had extremely dilated pupils, with normal blood pressure and vital signs. When Hofmann related his experiences to his colleagues, they were dubious that he had measured correctly, but to be safe, they took even lower doses. Each experienced what were later referred to as psychedelic mind "trips" [29].

In 1947, Sandoz began marketing and distributing LSD, under the brand name Delysid, as a possible psychiatric drug to treat neurosis, alcoholism, criminal behavior, and schizophrenia. In addition, LSD-25 was also used to treat autism and verbal misbehavior [28; 30]. In his book, Hofmann described how LSD helped provide relief to people who were dying of cancer and in severe pain for whom major analgesics were ineffective. He hypothesized that the analgesic effect was not inherent to the drug but was a result of patients dissociating from their bodies such that physical pain no longer affected them [29].

However, early studies on LSD did not always inform patients about the potential risks. For example, in some cases, patients with schizophrenia were given LSD and not told about the possible risk for a psychotic break [31]. Patients at the Addiction Research Center in Lexington, Kentucky, were often given the drug without being told what it was or the possible effects. Researchers who believed in the importance of "set and setting" (the patient's mindset and the setting where the drug was administered) were more likely to inform patients about possible risks and benefits. The 1962 Kefauver-Harris Amendments required that all patients provide informed consent for therapeutic interventions and research participation. Despite this, the "informed consent" of the 1960s was not as comprehensive as informed consent today. Some have posited that the primary goal was to release researchers from legal responsibility rather than to provide ensure the safety of patients and prospective subjects of clinical trials [31].

For about a decade, Hofmann and Sandoz believed that LSD might provide breakthroughs in psychiatry. However, with the major social change of the 1960s, characterized by protests for social change and against the Vietnam War and increasingly liberal attitudes regarding drugs among young people, the focus shifted to recreational rather than medical use of LSD, and in 1965, Sandoz stopped manufacture and marketing of LSD. In 1966, Sandoz gave their remaining supplies to the National Institute of Mental Health [31].

**Early Days of Psilocybin**

In 1957, Hofmann received a sample of dried *Psilocybe mexicana* mushrooms from a mycologist in Huautla de Jiménez in Oaxaca, Mexico. The mycologist, R. Gordon Wasson, had received a sample of the mushrooms and information regarding the sacred rituals of the Mazatec people from a curandera to whom he promised secrecy; this promise was obviously not kept, and Wasson's actions resulted in retaliation against the indigenous woman who he betrayed [138]. Hofmann used paper chromatography to separate the various components of whole extracts of mushrooms and ingested each separated fraction. The active fraction was then chemically characterized, crystallized, and named psilocybin. In 1958, Hofmann and his colleagues subsequently elucidated the structure and synthesis of psilocybin and psilocin, a minor component of the extract that is a dephosphorylated form of psilocybin. In the 1960s, Sandoz Pharmaceuticals began to distribute Indocybin, a psychotherapeutic drug in pill form, containing 2-mg psilocybin. This period also saw research focusing on psilocybin as a probe for brain function and recidivism and as an entheogen used by religious people (divinity students).

During this era, psilocybin, LSD, mescaline, and other psychedelics were used by some individuals with psychiatric diseases, and they were also used extensively by some psychiatrists to treat patients before the drugs were categorized as Schedule I of the U.N. Convention on Drugs in 1967, which preceded the Controlled Substances Act in the United States. Today, the medical value of hallucinogens is being tested in rigorous trials in settings such as Roland Griffith's Johns Hopkins research program. The experts from the psilocybin research group at Johns Hopkins University have described the importance of trained psychedelic therapists and other components of a psychedelic treatment session to optimize patient safety in hallucinogen research [32].

## CONSIDERING PSYCHEDELIC-ASSISTED PSYCHOTHERAPY AS A TREATMENT OPTION

For most mental health professionals, the idea of psychedelic-assisted psychotherapy is a major paradigm shift and leap from current practices of providing pharmacotherapy or psychotherapy to individuals or groups. At the same time, it may represent a new opportunity to combine the talents and skills of therapists with the proven benefits of a psychedelic drug. Combined psychotherapy/pharmacotherapy is the treatment of choice for most patients with mental health disorders, so interprofessional collaboration is a typical (and vital) part of treatment. Psychedelic medicine requires that diverse disciplines collaborate closely and communicate to clearly ensure that the therapy is safely and effectively administered.

## LEGAL AND REGULATORY BARRIERS

Today, the federal government has provided limited permission or even grants to study Schedule I drugs and their possible role in the treatment of patients. Outside of these limited cases, researchers find it difficult to obtain the needed drug for testing purposes. To avoid legal and regulatory issues, a good amount of research is performed outside of the United States.

## "SET" AND "SETTING" IN PSYCHOTHERAPY-ASSISTED PSYCHEDELIC TREATMENT

Since the 1960s, therapists have noted that the response to psychedelic drugs is impacted by the patient's mindset as well as the setting where the psychedelic drug is administered. For example, if the person feels confident that the experience will be a positive one, then this "set" is considered more conducive to a good experience while under the influence of a psychedelic drug compared with when persons are extremely apprehensive and fearful beforehand. By extension, if patients are in an office setting with a therapist or other practitioner with whom they feel safe, the outcome is generally better than in those who feel unsafe. Research has shown a better outcome with patients receiving psychedelics in a therapeutic setting versus receiving the drug while undergoing a positron emission tomography (PET) scan [33]. These researchers stated [33]:

> The finding that the PET environment was strongly associated with anxious reactions could be partially explained by the perceived atmosphere. Whereas non-PET experiments were mostly conducted in laboratory rooms that were furnished in an aesthetically pleasing way, the environment at the PET center was much more clinical and "antiseptic" (i.e., lots of technical equipment, white walls, personnel in white lab coats). Our results are therefore in support of current safety guidelines, which recommend avoiding "cold" and overly clinical environments in human hallucinogen research in order to reduce the risk of anxious reactions.

Another element of setting, and one that is also used to enhance set, is the use of music while the patient undergoes therapy with psychedelic medicine. Johns Hopkins has developed a "psilocybin playlist" lasting nearly eight hours that is used for patients who are undergoing treatment with psilocybin [34].

In many cases, psychedelic therapy is administered after a therapeutic session. Psychotherapy is often also provided during the course of the drug's effects and at integration sessions that occur after the drug was given to help the patient to give meaning and context for the experience [35]. This provision of multiple hours of psychotherapy over a short period of time can translate to higher costs. This scenario might be less appealing to insurance carriers than traditional therapies (e.g., antidepressants or other drugs), but this is yet to be seen.

It should also be noted that in some areas, there are clear manualized approaches to treating patients that carefully consider both set and setting; this is particularly the case for MDMA in the treatment of PTSD. However, these approaches are yet to be developed for most other psychedelic drugs. Again, this field offers burgeoning opportunities for psychiatrists, psychologists, primary care providers, and other mental health practitioners.

## ADVISING PATIENTS CONSIDERING PSYCHEDELIC MEDICINE

Some patients will approach their primary care providers to discuss the possibility of seeking care at a ketamine or MDMA (or other) clinic. It is important not to dismiss these treatment options out of hand. Instead, it may be best to ask the patients the following questions to help assess if the option would be helpful and if the facility is set up to provide optimal care:

- Who is the expert or experts running this clinic? What experience(s) make this person or team experts? What outcome data are provided?
- Does the patient have a severe and intractable diagnosis, such as treatment-resistant depression, substance use disorder, or PTSD? If not, then conventional medicine is still best.
- Does the clinic ensure professional observation after the drug is administered? This is always advisable in case the patient experiences adverse events.
- How soon after a drug is administered are patients discharged from the facility? Minimal times (e.g., 15 minutes) are not long enough to ensure safety.
- Does the facility offer psychotherapy before, during, and after the drug is administered? Combining psychotherapy with psychedelic medicine is the proven best practice.
- Is there a required follow-up?
- Are the costs for treatments clearly delineated? If not, patients should request, in writing, an estimate of total costs. Psychedelic medicine is likely not covered by health insurance and may be costly. Also, the cost may fluctuate significantly from one clinic to another.
- Has the patient experienced a psychotic break in the past or does the patient have first-degree relatives with a history of psychosis? Psychedelics have the potential to trigger an underlying predisposition for psychosis, although it can be temporary. Still, even a short-term psychotic break is a terrifying experience.

## ADDRESSING STIGMA

For many people, including some clinicians, the phrase "psychedelic medicine" evokes images of free love, 1960s counterculture, and recreational intoxication. In reality, these therapies typically look much more pedestrian, consisting of a patient sitting or lying on a couch while a clinician guides the person

**MAJOR PSYCHEDELIC RESEARCH CENTERS IN THE UNITED STATES**

**Johns Hopkins Center for Psychedelic and Consciousness Research**
https://hopkinspsychedelic.org

**National Institutes of Health Funding**
https://pubmed.ncbi.nlm.nih.gov/34624734

**Yale University**
https://medicine.yale.edu/psychiatry/education/residency/interest/psychedelic_science_group

**Mount Sinai**
https://www.mountsinai.org/about/newsroom/2021/mount-sinai-health-system-launches-center-for-psychedelic-research

**Stanford University**
https://med.stanford.edu/spsg.html

**University of California, San Francisco**
https://neuroscape.ucsf.edu/psychedelics

**Duke University**
https://dukepsychedelics.org

**University of Texas at Austin**
https://dellmed.utexas.edu/units/center-for-psychedelic-research-and-therapy

**Washington University in St. Louis (WUSTL)**
https://healthymind.wustl.edu/items/washington-universitys-program-in-psychedelic-research

**Harvard/Massachusetts General Hospital**
https://www.massgeneral.org/psychiatry/treatments-and-services/center-for-the-neuroscience-of-psychedelics

*Source: Compiled by Author* *Table 4*

through the experience in order to treat their severe psychiatric disorder. Although many of the drugs described in this course can and do induce hallucinations, subjects have reported that these experiences were integral and allowed them to resolve psychiatric issues that have been resistant to traditional treatments and that have significant impact on their lives. If further studies continue to bear these findings out, it would be unwise to ignore the benefits that may accrue.

## EMERGING PSYCHEDELIC TREATMENTS

The key psychedelic drugs actively being researched and/or currently in use today include psilocybin, ketamine, MDMA, ibogaine, kratom, LSD, mescaline, and ayahuasca (***Table 4***). In addition, nitrous oxide, a gas used for many years by dentists as both an anesthesia and analgesic for patients undergoing painful procedures, has also been found effective as a treatment for some psychiatric disorders.

### PSILOCYBIN

Beginning in the 2010s, psilocybin has been undergoing an era of increased research attention, and this compound remains under active investigation. Psilocybin occurs in nature in hundreds of species of mushrooms as 4-phosphoryloxy-*N*,*N*-dimethyltryptamine. However, when used by researchers, the drug is nearly always a chemically synthesized compound to maintain a standard dosage as well as the purity of the drug. In 2020, COMPASS Pathways announced that it had gained a patent in the United States for COMP360, its form of synthetically derived psilocybin [15].

According to a 2022 report from the Associated Press, some states, even in conservative areas (e.g., Utah), have approved studying psilocybin as a treatment. This movement has largely been driven by increasing rates of treatment-resistant PTSD among military veterans [36].

Psilocybin was first studied during the 1960s to establish its psychopharmacologic profile; it was found to be active orally at around 10 mg, with more potent effects at higher doses, with a four- to six-hour duration. Psilocybin is rapidly metabolized to psilocin, a full agonist at serotonin 5-HT1A/2A/2C receptors, with 5-HT2A receptor activation directly correlated

with human hallucinogenic activity. Time to onset of effect is usually within 20 to 30 minutes of ingestion. As a drug, it is about 20 times stronger than mescaline but much less potent than LSD [37].

In animal studies of the use of psilocybin, a link has been identified between reduced prefrontal mGluR2 function and both impaired executive function and alcohol craving. Psilocybin also restored healthy mGluR2 expression and reduced relapse behavior in mice [38]. Mice and humans do not always respond equivalently, but this finding may explain why psilocybin is effective in treating induced alcoholism in mice and provides an interesting research avenue in the investigation of psilocybin as a treatment for alcohol use disorder in humans, because relapse is a significant problem; even when a patient has abstained from alcohol for years, the underlying craving remains. If this craving could be reduced or altogether eliminated, this could revolutionize substance use disorder treatment.

In a study at King's College London, researchers studied the effects of psilocybin on the emotional and cognitive functions in healthy subjects in a Phase 1 randomized double-blind controlled study with 89 subjects (average age: 36.1 years). Subjects were randomized to receive placebo or 10 mg or 25 mg of psilocybin. Therapists were available to the subjects throughout the sessions. Six subjects at a time received the drug. The study showed that there were no short- or long-term adverse effects to the emotional processing or cognitive functioning of the subjects [39]. In this study, 70% of the subjects who received 25-mg psilocybin experienced visual hallucinations, compared with 60% of those who received 10-mg psilocybin and 6.9% of those who received placebo. The second most common treatment-emergent adverse event was illusion, which was experienced by 60% of subjects receiving 25-mg psilocybin and 63.3% of those receiving 10-mg psilocybin; 13.8% of those receiving placebo reported experiencing this effect. Other treatment-emergent adverse events reported more commonly among the treatment groups included mood alteration, headache, fatigue, and euphoric mood, all of which were lower or altogether non-existent in the placebo group. Also absent in the placebo group were auditory and tactile hallucinations [39]. The researchers concluded [39]:

> This study demonstrated the feasibility of one-to-one psychological support from specially trained therapists during [the] simultaneous administration of psilocybin in a supervised clinical setting in healthy volunteers. A single dose of psilocybin 10 mg or 25 mg elicited no serious adverse effects and did not appear to produce any clinically relevant detrimental short- or long-term effects, compared with placebo, in cognitive or social functioning or emotional regulation in this study in health volunteers.

In studies using psilocybin, the most common adverse reactions were found to be headache, nausea, and hypertension, and events were considered to be equivalent to those found with the use of SSRIs [40]. However, it should also be noted that the subjects in psilocybin clinical trials are usually screened for a family history of schizophrenia, major depression with psychotic features, high risk for suicide, and severe personality disorders before inclusion [40].

Another study at Johns Hopkins evaluated the efficacy and safety of psilocybin for the treatment of major depressive disorder. In this randomized study, 24 patients 21 to 75 years of age with moderate-to-severe unipolar depression were randomized to either immediate or delayed treatment. Subjects were administered two doses of psilocybin along with supportive psychotherapy. Researchers found a greater than 50% reduction in depressive symptoms, as measured by the GRID-Hamilton Depression Rating Scale (GRID-HAMD), in the treatment group. Before initiating psilocybin therapy, subjects first received six to eight hours of preparation with trained facilitators. The psilocybin was administered at doses of 20 mg/70 kg and 30 mg/70 kg, about two weeks apart, while subjects were in a comfortable room supervised by two facilitators. There were also follow-up counseling sessions [1]. The mean scores on the GRID-HAMD decreased from an average of 22.8 at the pretreatment level to 8.7 at 1 week, 8.9 at 4 weeks, 9.3 at 3 months, 7.0 at 6 months, and 7.7 at 12 months. These data indicate that the psilocybin provided persistent relief to many patients [1].

In a 2018 British study, 26 patients, 20 of whom were diagnosed with severe treatment-resistant depression, were administered separate doses of 10- and 25-mg psilocybin one week apart; administration took place in a supportive setting. Nineteen subjects completed the treatment process, including psychological support, and all of the completers reported improved symptoms based on Quick Inventory of Depressive Symptoms (QIDS-SR16) and HAM-D scores. Four patients experienced remission of their depression at week five. Many completers continued to benefit from treatment at three months and six months. Suicidality scores among the patients also significantly fell within the two weeks after treatment [41].

Not all researchers have offered a ringing endorsement of the use of psilocybin. A 2021 study studied 59 patients with moderate-to-severe major depressive disorder. The subjects were administered either two doses of 25-mg psilocybin three weeks apart plus placebo (30 patients) over six weeks, or they were given escitalopram (an SSRI) for six weeks (29 patients). All the patients also received psychological assistance. No significant differences were noted in depression symptoms between the two groups, and the researchers concluded that further studies with larger populations were needed. Even the adverse events in the two groups were somewhat similar; the

most common adverse effect in both groups over the course of the study was headache, followed by nausea [42]. Even in this study, psilocybin was about as effective as antidepressant therapy. This is remarkable, in that this new treatment is about as effective as the established criterion standard treatment for major depressive disorder.

Although studies have supported the hypothesis that psilocybin provided under research conditions by physicians has a positive effect on depressive symptoms, until recently, the mechanism by which this improvement has occurred was largely unknown. However, in a study of 16 individuals with treatment-resistant depression, researchers used functional magnetic resonance imaging (fMRI) to assess functional brain changes both at baseline and one day after the study group received 25-mg psilocybin. The researchers found brain network modularity was reduced within just one day after the psilocybin was administered [43]. In a second study by the same researchers, 59 patients with major depressive disorder were randomized to either two doses of 25-mg psilocybin three weeks apart plus six weeks of daily placebo or to six weeks of 10- to 20-mg escitalopram per day plus 1-mg psilocybin (an ineffective dose). In this study, 29 subjects were in the escitalopram arm, although the group ultimately decreased to 21 subjects (28% dropout rate). The 30 patients in the psilocybin group decreased to 22 subjects (27% dropout rate) [43]. The researchers noted that [43]:

> It is plausible that this putative liberating effect of psilocybin on cortical activity occurs via its direct agonist action on cortical 5-HT2A receptors, dysregulating activity in regions rich in their expression. We surmise that chronic escitalopram does not have the effect on brain modularity due to its more generalized action on the serotonin system and predominant action on inhibitory postsynaptic 5-HT1A receptors, which are richly expressed in limbic circuity.

The researchers found that the antidepressant effect of the psilocybin was sustained and rapid and that it also corresponded with decreases in fMRI brain network modularity. This indicates that the antidepressant effect of psilocybin, when it works, is linked with a global increase in brain network integration. In contrast, the response to the escitalopram was mild and caused no changes to the brain network [43].

## KETAMINE

Ketamine is a derivative of phencyclidine (PCP), which itself was originally developed as an anesthetic. However, the major adverse effects of PCP, such as aggression, psychosis, and dysphoria, made it an undesirable and unacceptable anesthetic choice [44]. In contrast, ketamine was effective as an anesthetic and had few adverse effects. PCP subsequently became a drug of abuse.

While ketamine has been used in operative analgesia for decades, it has also become a drug of abuse and misuse [45]. Most notoriously, ketamine became known as a "date-rape drug," because it was administered in drinks to unknowing victims who were subsequently sexually assaulted by their predators. Because ketamine causes amnesia, victims have little or no memory of what occurred to them, although they often experienced after-effects, such as pain. As a result of this growing criminal use, Congress passed the Drug-Induced Rape Prevention and Punishment Act of 1996. During this period and the decade following, there was increased awareness of the dangers of ketamine and other drugs that were used in a similar manner, such as flunitrazepam (Rohypnol) and gamma hydroxybutyric acid (GHB) [46]. As a result, ketamine developed a stigma, and this negative view may persist in many minds.

Ketamine is a Schedule III drug that is a combination of s-ketamine (esketamine) and r-ketamine (arketamine). In 2019, the use of esketamine as a nasal spray (brand name Spravato) was approved by the FDA for the treatment of treatment-resistant depression. Since then, it has also been approved to treat suicidal depression. However, it should be noted that this nasal spray formulation is not available at most pharmacies; instead, it is provided solely through a restricted distribution system. The FDA also requires that patients be overseen for a minimum of two hours after treatment, in order to allow sufficient time to identify and address and adverse reactions that develop in patients. (It is not clear if all ketamine clinics adhere to this provision.)

EVIDENCE-BASED PRACTICE RECOMMENDATION

For patients with major depressive disorder who have not responded to several adequate pharmacologic trials, the Department of Veterans Affairs suggests ketamine or esketamine as an option for augmentation.

(https://www.healthquality.va.gov/guidelines/MH/mdd/VADoDMDDCPGFinal508.pdf. Last accessed July 8, 2022.)

**Strength of Recommendation**: Weak for

After treatment with ketamine, patients should not leave the facility until they are cleared to do so by a healthcare provider and they should also be cautioned to avoid driving or using heavy equipment until the following day. In addition, patients are not allowed to take the nasal spray home, because it may only be used in the medical office while under the supervision of qualified staff members [47].

Intravenous ketamine has been used off-label for treatment-resistant depression by some clinicians, and ketamine clinics are established in many parts of the United States, although their fees vary widely. The effects of intravenously administered ketamine may last for hours, days, or even weeks in some patients. Some believe that intravenous ketamine is significantly more effective than its intranasal form because it includes both the s and r forms of the drug.

Some researchers have found that the mental state of the patient (set) prior to receiving treatment with ketamine may affect the outcome of treatment. In a 2019 study, 31 patients with major depressive disorder were treated with ketamine infusions. Researchers used multiple instruments to measure the mental state of subjects prior to and after receiving treatment, including the Montgomery-Asberg Depression Rating Scale (MADRS) and the Beck Hopelessness Scale. In this study, 17 subjects (55%) responded to the ketamine, while 14 (45%) had no response [48]. Non-responders had significantly higher rates on anxiety scales than responders. The researchers stated [48]:

> The present study showed for the first time that non-responders had more anxiety-related experiences induced by the first ketamine infusion than responders confirming our initial hypothesis of significantly different subjective experiences as a function of treatment response. Specifically, we found that it was the extent of ketamine-induced anxiety that was negatively predictive of a treatment response after a series of six infusions on average.

They also noted that providing a calm treatment environment to patients might be sufficient to reduce anxiety levels in patients to improve outcomes. This is the goal of treatment providers as well as researchers who emphasize the importance of set (mindset) and setting, as discussed. In this study, there was no follow-up after the last infusion, which may also have improved efficacy [48].

In another study of 30 individuals with PTSD of a median duration of 15 years, half of subjects were randomized to a ketamine group and half were assigned to a midazolam (a benzodiazepine) group. The subjects received six infusions over the course of two weeks of either ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg). The subjects were evaluated with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) at baseline and also at the end of treatment [49].

The average CAPS-5 total scores following the infusions were 11.88 points lower among the subjects in the ketamine group compared with the midazolam group. About two-thirds of the ketamine subjects (67%) responded to the treatment, versus only 20% of treatment responders in the midazolam group. The median time to loss of treatment following the two-week ketamine treatment period was 27.5 days. However, in outlier cases, two subjects still had not lost their response; improvements continued at 50 days and 102 days since the last infusion. The ketamine group experienced a major reduction in symptoms of depression as well as in clinical ratings of global psychiatric illness severity. The researchers concluded that the findings from this study support the assertion that "repeated ketamine infusions are safe and generally well tolerated among individuals with chronic PTSD, with only transient emergence of psychoactive and hemodynamic side effects" [49].

In a French study, ketamine was explored as a treatment for individuals with severe suicidal ideation in a double-blind randomized clinical trial. In this six-study report, published in 2022, 156 patients were given either a 40-minute infusion of ketamine or placebo (saline solution). The administration was repeated 24 hours later. The groups were also divided into subjects with bipolar disorder, depressive disorder, and other diagnoses. Of patients in the ketamine group, 93.1% had a past history of the commission of a suicidal act, as did 86.6% of the subjects in the placebo arm [50].

On day 3, nearly two-thirds (63%) of the patients in the ketamine group achieved full remission from suicidal thoughts. In contrast, 31.6% of the patients in the placebo group were in remission. In nearly 44% of the ketamine subjects, remission occurred within two hours after the first infusion, compared with 7.3% of the placebo group. Ketamine was particularly effective in the bipolar group, while its effect was not significant in the group with major depressive or other psychiatric disorders. The researchers speculated that ketamine might provide an analgesic kind of effect to mental pain [50].

**MDMA**

In the past and even to date, MDMA (also referred to as "Ecstasy" or "Molly") has been largely a drug of abuse. According to the National Institute on Drug Abuse, about 2.6 million people in the United States 12 years of age and older reported past-year use of MDMA in 2020 [51]. The drug was originally developed by Merck in 1912, and in the 1970s, it was found to be useful in combination with psychotherapy [52]. However, because of considerable active abuse of the drug in the United States, in 1985, MDMA was categorized as a Schedule I drug under the Controlled Substances Act in an emergency ban, and consequently research on this drug largely halted until the 2010s [53].

Today, researchers have demonstrated the efficacy of combination psychotherapy and MDMA in treating PTSD. The FDA has granted "breakthrough therapy" permission for MDMA therapeutic treatment, largely as a result of the findings of several small studies. Clinicians who use MDMA-assisted psychotherapy to treat individuals with PTSD have access to a manual outlining best practices for this therapeutic use. In the 2017 revision of this manual, the following explanation is given [54]:

> The basic premise of this treatment approach is that the therapeutic effect is not due simply to the physiological effects of the medicine; rather, it is the result of an interaction between the effects of the medicine, the therapeutic setting, and the mindsets of the participant and the therapists. MDMA produces an experience that appears to temporarily reduce fear, increase the range of positive emotions toward self and others, and increase interpersonal trust without clouding the sensorium or inhibiting access to emotions. MDMA may catalyze therapeutic processing by allowing participants to stay emotionally engaged while revisiting traumatic experiences without being overwhelmed by anxiety or other painful emotions. Frequently, participants are able to experience and express fear, anger, and grief as part of the therapeutic process with less likelihood of either feeling overwhelmed by these emotions or of avoiding them by dissociation or emotional numbing. In addition, MDMA can enable a heightened state of empathic rapport that facilitates the therapeutic process and allows for a corrective experience of secure attachment and collaboration with the therapists.

In six double-blind, randomized clinical studies conducted between 2004 and 2017, 72 subjects are administered 75–125 mg of MDMA in two or three sessions, comparing these results with 31 patients who received placebo; all the patients had diagnosed PTSD. The drug was administered following 90-minute sessions of psychotherapy and three to four therapy sessions were also provided during follow-up after MDMA therapy [55].

Members of the treatment group reported significantly reduced scores on the CAPS-5 compared with the control group. In addition, after two sessions, 54.2% of those who received MDMA no longer met the criteria for PTSD—they were in remission. In contrast, only 22.6% of the control group experienced remission. The researchers noted that "MDMA-assisted psychotherapy was efficacious and well tolerated in a large sample of adults with PTSD" [55].

In another randomized, double-blind, placebo-controlled phase 3 clinical trial with 90 individuals with severe PTSD, the subjects received manualized therapy with either MDMA or placebo. Three preparatory sessions occurred before the administration of the drug, and there were nine integrative therapy sessions afterwards. Subjects in the MDMA treatment group experienced a significant decrease in CAPS-5 (-24.4) scores compared with placebo subjects (-13.9). Scores on the Sheehan Disability Scale (SDS) also significantly improved in the MDMA subjects compared with the placebo subjects [56].

The researchers noted [56]:

> Given that PTSD is a strong predictor of disability in both veterans and community populations, it is promising to note that the robust reduction in PTSD and depressive symptoms identified here is complemented by a significant improvement in SDS score (for example, work and/or school, social and family functioning). Approximately 4.7 million U.S. veterans report a service-related disability, costing the U.S. government approximately $73 billion per year. Identification of a PTSD treatment that could improve social and family functioning and ameliorate impairment across a broad range of environmental contexts could provide major medical cost savings, in addition to improving the quality of life for veterans and others affected by this disorder.

Because major problems with sleep quality are common among patients with PTSD, some researchers have studied the effects of MDMA-assisted psychotherapy to determine its effects on sleep disorder. In a series of four studies with 63 subjects at sites in the United States, Canada, and Israel, subjects were randomized to two or three sessions of MDMA-assisted psychotherapy or to a control group. PTSD symptoms were assessed with the CAPS-IV, and the Pittsburgh Sleep Quality Index (PSQI) was used to measure changes in sleep quality. At the conclusion of the study, the CAPS-IV severity scores had decreased by 34 points in the MDMA group, compared with a decrease of 12.4 points for the control group. In addition, sleep quality improved significantly in the experimental group compared with the control group. In the treatment group, 53.2% of subjects reported a PSQI score drop of 3 or more points, compared with 12.5% in the control group [57].

Although there appears to be a benefit for MDMA therapy in the management of PTSD, especially for patients who have failed other therapies, the durability of this affect has been questioned. One study indicated improvement may be persistent for a considerable period of time for some subjects. In a study involving 107 subjects with PTSD, individuals were administered either two or three doses of MDMA (75–125 mg) during blinded or open-label therapy sessions. The subject's PTSD symptoms were evaluated 1 to 2 months after the last MDMA session and again after 12 months. The researchers reported that at the 12-month follow-up time, nearly all (97.6%) of the subjects said they had benefited from the treatment, and 53.2% reported large benefits that had lasted or even increased. A minority of subjects reported unfavorable results; 8.4% reported harms. However, in 86% of these cases (six of seven subjects), the harms were rated as a 3 or less on a 5-point scale. There were no reports of severe harm, and all the subjects who reported harm also reported one or more benefits. The most common harm reported was worsened mood (3.6%) [58]. The researchers noted that, "Overall findings from the present analyses support MDMA-assisted psychotherapy as an

efficacious treatment for PTSD with symptom improvements that were sustained at 1 to 3.8 years post-treatment. These findings corroborate and expand preliminary results from the first phase 2 trial of this treatment" [58].

**IBOGAINE**

Largely derived from the Western African shrub *Tabernanthe iboga,* ibogaine has been explored as a possible treatment for opioid use disorder, although there are many caveats to be considered, including the fact that ibogaine is a Schedule I drug. Given the current climate surrounding opioid misuse and use disorder in the United States, possible treatment options are a major focus. According to the Centers for Disease Control and Prevention, more than 70% of drug overdoses in the United States in 2019 were related to opioid use [59]. Ibogaine apparently acts to eliminate craving for opioids and rapidly detoxifies individuals with opioid dependence, although much further study with larger populations is needed. Most people who seek treatment with ibogaine have opioid use disorder, but some have been dependent on stimulants such as cocaine.

The anti-addictive capabilities of ibogaine were first noted by Howard Lotsof in 1962 as a result of his own experience with the drug as well as reports from others. Lotsof, a man in recovery from heroin use disorder from New York City who unexpectedly found relief and remission with ibogaine, subsequently actively and tirelessly lobbied researchers to study the drug. He eventually succeeded, and multiple researchers using both animal and human studies have demonstrated ibogaine's apparent ability to induce recovery in some persons struggling with substance use disorders [60; 61].

Metabolism of ibogaine is purportedly mediated by the p450 cytochrome enzyme CY2D6. Because of genetic differences, an estimated 10% of persons of European heritage (predominantly White Americans in the United States) lack the necessary gene to synthesize this enzyme. Among this group, including the many individuals who do not realize they lack this gene, administration of ibogaine can result in plasma levels as much as twice as high as those in persons with the gene. As a precaution, a test dose of the drug may be given to subjects to assess the response. Another option is genotype screening of subjects who seek treatment with ibogaine, to ensure safety and to aid in treatment decisions [62].

Although it provides insufficient data from which to draw major conclusions, a study of the use of ibogaine in two adults with opioid use disorder is interesting. The experiences of one of the patients are described here, although it should be noted that both patients have remained abstinent for several years [62]. The first patient developed an opioid use disorder secondary to pain from chronic pancreatitis. His physician was concerned about potential misuse and weaned the patient off opioids; however, the patient began taking large quantities of oxycodone tablets he purchased illegally. As the substance use disorder progressed, this patient was actively resistant to conventional treatment despite clear physical and psychosocial consequences. Eventually, he agreed to experimental treatment with ibogaine.

The patient was screened with an electrocardiogram prior to treatment and administered a test dose of ibogaine. During the first four days of treatment, he was administered oxycodone (legally obtained via prescription). The opioid doses were steadily titrated down and on day 4, all opioid medications stopped. During this same period, the patient was given increasing doses of ibogaine. On day 4, the patient was given a "flood dose" of both iboga and ibogaine (variations of the same drug). Between treatments, diazepam was given to support sleep and assuage anxiety. Treatment lasted for six days, and the patient remained at the clinic for a total of eight days. At three-year follow-up, the patient had remained abstinent from opioids, as indicated by negative drug screens. Interestingly, after the flood dose of ibogaine, the client also reported that his chronic pain issues ended, and they have not recurred [62]. The reasons for this finding are unknown.

In a study of 14 individuals with opioid use disorder, subjects were given staggered doses of 200-mg ibogaine capsules at two different clinics. Because ibogaine is a stimulant, most patients were given benzodiazepines or sleep aids so they could attain sufficient hours of sleep. The first dose administered was a test dose given when the patient was in a withdrawal state from opioids; then, a larger dose of up to 600 mg of ibogaine was given one to four hours later. This was followed by smaller dosages of 200 mg given at 20-minute intervals until ended by the provider. The subjects were interviewed pretreatment, immediately post-treatment, and 12 months later. The outcome was that 12 of the 14 subjects (85.7%) had either a marked reduction in opioid use or ended use of the drug altogether [61].

In a larger study of 191 adults wishing to detoxify from opioids or cocaine, a single dose of ibogaine was administered during a medically supervised period of detoxification. According to the researchers, the goals of the study were to safely detoxify the subjects from opioids or cocaine, to provide motivational counseling, and to refer the patients to aftercare and 12-step programs [63]. All subjects received a physical examination, and a medical history was taken. Laboratory tests were administered, as were electrocardiograms. The subjects were drug tested at the beginning of the program, and all tested positive for either opioids or cocaine. A licensed therapist worked with the subjects during and after ibogaine was administered. The average age of subjects was 36 years, and all were habitual users. The subjects were given one dose oral (gel capsule) ibogaine 8–12 mg/kg. In this study, the most common adverse effect was headache, reported by 7% of the subjects; orthostatic hypotension occurred in 5% of the subjects. About 2% of adverse events were considered to be moderately severe.

After the ibogaine was administered, its effects began about 30 to 45 minutes later. According to the researchers [63]:

> Sensory and perceptual changes included reports of visual images, changes in the quality and rate of thinking, and heightened sensitivity to sound. Most subjects reported a dream-like experience lasting between four and eight hours, after which there was an abrupt change in the sensory experience to a more quiet period of deep introspection.

Approximately 92% of subjects reported benefits from the experience. They also reported that both drug craving and depression symptoms improved with doses of 500–1,000 mg. One shortcoming of this study, however, was a lack of follow-up. It would be especially helpful to know if these individuals remained abstinent 6 to 12 months later. Unfortunately, this was not among the goals of the researchers [63].

Ibogaine is difficult to obtain in the United States, and travel to other countries to obtain treatment has been reported, which can be very costly. Assuming that ibogaine were to be equal in efficacy to clonidine or lofexidine for detoxification from opioids or acute discontinuation, it is still unclear what long-term effects or level of continued abstinence can be expected. Naltrexone (Vivitrol) following detoxification might be facilitated. But, data supporting the use of suboxone and methadone in reducing overdoses, deaths, and emergency department visits are clear, including both short- and long-term outcomes. It is important to compare ibogaine to buprenorphine or methadone treatment, just as psilocybin was compared to SSRI therapy [64].

## KRATOM

Kratom is a drug derived from *Mitragyna speciosa,* an evergreen tree native to Southeast Asia, where it has been used for generations, largely by locals who chew on the leaves or brew it into a tea and reportedly use the drug for an energizing purpose (e.g., to facilitate longer work periods), much as Americans use caffeine. Kratom is used by consumers in the United States as a drug of abuse and, less commonly, to manage depression. As of 2022, the drug is not scheduled by the U.S. Drug Enforcement Administration (DEA), although the DEA did consider categorizing kratom constituents mitragynine and 7-hydroxymitragynine under Schedule I in 2016. This effort was met with considerable resistance and was abandoned. As such, the product remains available locally in smoke and "head" shops, although many purchase the drug over the Internet. Kratom is banned in six states, including Arkansas, Indiana, Tennessee, Vermont, Wisconsin, and most recently in Alabama [65].

Experts exploring the potential psychiatric uses of kratom have expressed optimism. According to McCurdy, kratom "seems to have mood lifting and elevating properties in addition to its ability to seem to move people off of hardcore opiates" [66]. Although the drug is traditionally used as a stimulant, it has a sedative or opioid-like effects in very high doses. It has been hypothesized that kratom might have a role in the treatment of opioid use disorder, although much more study is needed.

It is important to note that kratom products available in the United States are very different from those that are used by people in their native environments. For example, the kratom used in Southeast Asia is almost always derived from fresh leaves, while in the United States, the products are freeze-dried leaves, concentrated extracts, or liquid "energy shots." As a result of these differences, concentrations and adulteration are concerns. Some individuals in the West who consume kratom products have displayed blood serum levels of mitragynine (the key alkaloid in kratom) 100 to 1,000 times higher than in those found in consumers in Southeast Asia [67].

Another issue is one of purity. In an analysis of eight samples of the drug, researchers found that all the samples tested positive for varying levels of *Mitragyna,* ranging from 3.9–62.1 mg/g, which is a wide range that could significantly alter efficacy and toxicity [68]. In addition, six of the samples tested positive for fungi and bacteria. Most (seven) of the samples were positive for significant levels of toxic heavy metals, including nickel, lead, and chromium. The presence of lead was particularly troubling, as lead has many potentially toxic effects, particularly in terms of potential problematic neurologic effects in children and young adults as well as a variety of cognitive, developmental, immunologic, renal, and cardiovascular effects [68]. Although this study did not find evidence of *Salmonella* contamination, in 2018, a *Salmonella* outbreak originating from kratom products was reported to affect 199 people spanning 41 states [69]. It is clear that the purity of kratom purchased in the United States is highly questionable, largely because there are no federal constraints on its production by the FDA or other federal agencies. Healthcare professionals who know or suspect that their patients are using kratom may wish to warn them about these findings.

## LSD

As discussed, LSD is a compound synthesized from ergot. It is usually administered as an oral solution. LSD takes effect within 20 to 40 minutes after ingestion, and its effects may last for up to 12 hours. Flashbacks may also occur with this drug, defined as a feeling of re-experiencing an event or emotion that occurred during the course of the LSD "trip." LSD is about 2,000 times more potent than mescaline [37].

Prior to the Controlled Substances Act passage in 1970, there were numerous research studies on LSD as a treatment for depression, substance use disorder, and other psychiatric diagnoses, although some of these studies were not scientifically rigorous by today's standards. Fewer studies on LSD are published today, but several merit some attention. For example, a 2022 study assessed the impact of LSD on stressed mice [70]. Anxious mice were administered low doses of LSD for seven days, during which their anxiety levels decreased. In addition, researchers found that the mice given LSD showed signs of increased production of new dendritic spines, a sign of brain plasticity. The researchers also found that the LSD increased the production of serotonin in the treated mice, in a somewhat similar manner to SSRI antidepressants [70].

In an earlier study of the effects of LSD on humans with life-threatening diseases, 8 of the 12 subjects were given 200 mcg of LSD and a control group was given 20 mcg, an insufficient dose to generate significant response. After the initial blinded study was unmasked, the control group subjects were also given 200 mcg of LSD. All subjects had a score of higher than 40 on the state or trait scale of the Spielberger State-Trait Anxiety Inventory before the study. In addition, half the subjects had diagnosed generalized anxiety disorder. A therapist was present for two sessions conducted two to three weeks apart. The experimental sessions lasted eight hours, and patients left only to use the restroom [71]. Subjects who received the 200-mcg dose of LSD displayed a decrease in anxiety as measured by multiple instruments, and this decrease persisted at the 12-month follow-up evaluation. Overall, the subjects experienced a 78% drop in anxiety scores and a 67% increase in quality of life scores after one year. They also reported better access to and control of their own emotions [72].

While this research is interesting and points to areas for future research, it remains to be seen if LSD (or a similar compound) will ever be in clinical use for anxiety and depression. In addition to overcoming stigma and issues with adverse effects, significant additional research on efficacy is necessary.

## MESCALINE

3,4,5-trimethoxyphenethylamine, also known as mescaline, is a psychedelic drug that is mainly found in *Lophophora williamsii*, or the peyote cactus. Its effects upon ingestion are similar to the effects found with LSD or psilocybin, including hallucinations and euphoria [37]. The drug is known to have been used for thousands of years for these and perceived spiritual or medical effects; archaeologists have found evidence of this drug in Texas dating back 5,700 years [73]. Today, it is a Schedule I drug, but it may be used legally in religious ceremonies of the Native American Church. Mescaline has been suggested as a potentially effective treatment for a variety of mental health conditions, including depression, OCD, anxiety, and substance use disorder; however, research has yet to be conducted to support these claims.

The average dose of mescaline ranges from 20–500 mg, and the duration of action is about 10 to 12 hours. Individuals suffering from mescaline toxicity (typically seen with doses of 20 mg/kg or greater) may experience tachycardia, hypertension, seizures, hyperthermia, respiratory depression, and rarely death [73]. Concomitant use of mescaline with stimulant drugs (e.g., nicotine, cocaine, ephedrine, amphetamines) may increase the risk of adverse central nervous system effects.

In a survey of 452 individuals who reported using mescaline, researchers found that the drug was usually used once per year or less frequently, and only 9% of users reported a craving for mescaline. About 50% of users reported established psychiatric diagnoses, including anxiety and depression, and of this group, more than 65% reported that these problems improved after taking mescaline [74]. Clinical studies are necessary to confirm or refute these findings.

In another analysis of these data, nearly 50% of respondents reported their experience with mescaline was either the most meaningful experience of their lives or in the top five most meaningful experiences. Respondents who said they had experienced improvement in psychiatric problems were significantly more likely to also report experiencing mystical/spiritual experiences and psychological insight [75].

## NITROUS OXIDE

Nitrous oxide (chemical formula $N_2O$) is a component familiar to many, as it is commonly used today to facilitate comfort and address anxiety in dental settings. Historically, it has been used in both dental and medical interventions. The origins of nitrous oxide are attributed to Joseph Priestley's discovery in 1772, who referred to it as "dephlogisticated nitrous air" [76]. Anesthetic use of nitrous oxide was discovered by a dentist in 1844, and it was used for this purpose almost solely until the 1980s. The first research into the use of nitrous oxide for neuropsychiatric purposes was published between 1920 and 1950, and in the early 1980s, low-dose titration of nitrous oxide was introduced into medical practice as a possible adjunct to the treatment of psychiatric disorders, including substance use disorders [77]. Before then, it was limited to use as an anesthetic or for analgesia during childbirth. In 1994, the term psychotropic analgesic nitrous oxide was introduced in order to better distinguish anesthetic and nonanesthetic preparations [77].

The anxiolytic action of nitrous oxide is believed to be due to binding at select gamma-aminobutyric acid (GABA) receptors, an action similar to the benzodiazepines [78]. The mild analgesic effect appears to be linked to the endogenous opioid receptor system, as experimental studies have shown that the introduction of opioid receptor antagonists to the brain decreases the analgesic efficacy of nitrous oxide [79].

The route of administration is inhalation via a mask secured to the patient's nose. In the dental setting, the concentration of nitrous oxide is 25% to 50% (usually 30% to 40%) nitrous oxide with oxygen. When utilized in obstetrics, a fixed 50% concentration with oxygen is used [77]. Onset of action can occur in as quickly as 30 seconds, with the peak effects seen in five minutes or less. Unlike the benzodiazepine medications, nitrous oxide is not metabolized in the body. It is eliminated via respiration within minutes after 100% oxygen is inhaled at the conclusion of the intervention [78]. Repeated doses could be problematic, as extended use of nitrous oxide has been linked to vitamin B12 deficiency [76]. As such, serum vitamin B12 level may need to be measured before and after treatment.

Nitrous oxide has been demonstrated to improve the condition of individuals with treatment-resistant depression. A study of 20 subjects with treatment-resistant depression were randomly placed in either a nitrous oxide treatment group (10 subjects) or placebo group (10 subjects). The nitrous oxide group inhaled 50% nitrous oxide/50% oxygen, and the placebo group received 50% nitrogen/50% oxygen. There were two sessions one week apart. At the end of the study, four patients (40%) had a decrease in symptoms of depression and three patients (30%) experienced full remission. In contrast, one patient improved after receiving the placebo (10%) and none of the placebo patients remitted from their depression. The improvements in the nitrous oxide group were rapid, occurring in some cases within as little as two hours of receiving the drug [80]. Adverse events were mild and included nausea and vomiting, headache, and dizziness/lightheadedness. At the time of the second session, some patients in the treatment group experienced a carryover effect from the first week's treatment, as evidenced by sustained improvements in their scores on the Hamilton Depression Rating Scale (HDRS-21).

A separate study was undertaken to determine whether a single solution of 25% nitrous oxide would be as beneficial as a 50% solution. This study included 24 subjects with treatment-resistant depression who were randomly placed in one of three groups. Each group received either 50% nitrous oxide therapy, 25% nitrous oxide therapy, or placebo each month; each patient had the opportunity to receive all three treatments. At the end of the study, 55% of the subjects reported improvement in at least half of their symptoms, while 40% reported full remission [81]. Of interest, the 25% nitrous oxide solution had about the same level of efficacy in reducing depression as the 50% solution; however, there were significantly lower levels of adverse events in the 25% group. For example, 21% of those who had received 50% nitrous oxide concentration reported nausea; this decreased to 5% in the group that received 25% concentration. Further, the incidences of headache and dizziness were 17% and 13%, respectively, in the 50% concentration group, while the rates were 10% and 0% in the 25% group [82].

The study made it clear that with nitrous oxide, a 25% solution administered over one hour could improve treatment-resistant depression. Most of the study patients had failed an average of 4.5 antidepressants before the study, so the results were significant for a group in need of additional treatment options.

**AYAHUASCA/DIMETHYLTRYPTAMINE (DMT)**

Ayahuasca is a brew derived from the leaves of *Psychotria viridis*, a shrub found in Amazonian South America, and which contains DMT, a hallucinogenic alkaloid. The brew is also made with the *Banisteriopsis caapi* vine, the bark of which contains ingredients that act as MAO inhibitors.

In a Brazilian study involving 29 subjects with treatment-resistant depression, patients were randomized to receive a dose of either ayahuasca or placebo. Subjects were evaluated on the MADRS at the following points: baseline, day 1, day 2, and day 7 after dosing. They found MADRS scores were significantly lower in the ayahuasca group at all points and all individuals in this group experienced improvements. In contrast, 27% of patients in the placebo group developed worse depression symptoms. However, ayahuasca sickens many people, and most of the subjects who were given this substance felt nauseous and 57% vomited [83].

In another small Brazilian study, six subjects with recurrent major depressive disorder (without psychotic symptoms) were assessed for response to ayahuasca therapy. All individuals were inpatients at a psychiatric unit and were not taking any psychiatric or recreational drugs. The ayahuasca used by the volunteers was plant-based and refrigerated before the study, and each person drank 120–200 mg [84]. All subjects experienced decreases in depression symptoms on days 1 and day 7 of treatment. There were significant decreases in the Brief Psychiatric Rating Scale (BPRS), indicating improvements in both depression and anxiety. There were also statistically significant decreases in scores on the HAM-D and the MADRS. For example, on day 1, there was a 62% decrease on the HAM-D, and a 72% decrease by day 7. On day 14, however, depression symptoms increased. Similar changes were seen with the MADRS scores [84]. About half the volunteers did vomit; however, vomiting did not appear to impact the efficacy of the drug [84]. If ayahuasca is to be considered as a therapeutic option, a way to counteract the emetic effects and make the drug more tolerable to patients is necessary. To date, experts have hypothesized that antiemetic drugs might interfere with the action of ayahuasca.

Another problem with the scientific study of ayahuasca is that the effects of the drug depend on the concoction and there are no standardized dosages. If the drug could be provided in a synthesized form, it would become easier to evaluate and study in patients with depression and other disorders. In Barker's report on DMT, he states [85]:

> While ayahuasca obviously holds promise in many social, cultural, and therapeutic paradigms, including treatment of addiction, anxiety, and depression in psychiatry and many other possible applications, it is, nonetheless, a complex mixture of perhaps thousands of compounds.

DMT has been identified in additional substances. The Sonoran Desert toad (*Bufo alvarius*), native to Texas, California, and Mexico, excretes a venom when threatened that contains a naturally occurring form of DMT. This venom, which can be made into crystals and smoked, is popular for inducing psychedelic trips among recreational users. However, this venom is unsafe, and some have died after smoking it. Further, harvesting this venom has reduced the population of the toad in some areas. Overall, experts recommend that people not attempt to capture the toads or harvest the venom [86].

## DIAGNOSES AND PSYCHEDELIC MEDICINE

This section will outline the possible role of psychedelics in the management of specific psychiatric diagnoses, including diagnoses not previously discussed. It is important to remember that most of these uses are investigational.

### TREATMENT-RESISTANT DEPRESSION AND SUICIDE

Depression and suicidal depression are major problems in the United States. As noted, at least 30% of persons with depression do not respond to psychotherapy and/or medication. Psilocybin has proven effective at providing breakthroughs with treatment-resistant depression as well as in treating suicidal depression [41; 42]. Nasal spray esketamine (Spravato) is FDA-approved as an adjunct treatment in addition to a conventional antidepressant for treatment-resistant depression and/or major depressive disorder with suicidal ideation or behavior [87]. The nasal spray formulation of esketamine is administered in two sprays (28 mg) per device. The recommended dosage for adults with treatment-resistant depression is 56 mg on day 1, then 56 – 84 mg twice per week for four weeks, reducing to once per week for the next four weeks, and then once weekly or once every two weeks thereafter. This drug is only administered under medical supervision, and patients should remain under observation for at least two hours following administration.

There are concerns regarding misuse, excessive sedation, and diversion, and a Risk Evaluation and Mitigation Strategy (REMS) has been established. The full document is available online at https://www.accessdata.fda.gov/drugsatfda_docs/rems/Spravato_2022_01_03_REMS_Document.pdf.

### PTSD

MDMA and ketamine are well on their way to being proven safe and effective in the treatment of PTSD, and further studies on other psychedelics are likely to provide even more breakthrough information. According to the National Center for PTSD, an estimated 12 million adults in the United States have PTSD in a given year; 8% of women and 4% of men develop PTSD in their lifetime [88]. However, PTSD is very difficult to treat with medications and psychotherapy.

The usual dosage of ketamine for the treatment of persistent PTSD is 0.5 mg/kg given via a 40-minute IV infusion. The regimen typically consists of multiple sessions per week for two to four weeks [89].

In the research setting, MDMA for PTSD is typically given during or immediately preceding a psychotherapy session. The usual dose is 75–125 mg in a single dose [90]. As a Schedule I drug, MDMA is only used in clinical trials and research settings.

### SUBSTANCE USE DISORDERS

To date, psychedelic drugs such as ibogaine have not been proven effective in treating opioid use disorder and may not compare well to existing and approved treatments. However, limited studies have shown decreased substance use after administration of psilocybin and ketamine. A 2014 open-label pilot study married a 15-week smoking cessation program with several doses of psilocybin. This study included 15 smokers who were considered psychiatrically healthy adults who had smoked an average of 19 cigarettes per day for an average of 31 years [91]. Psilocybin was administered during the 5th, 7th, and 13th week of the study. During the first four weekly meetings, cognitive-behavioral therapy was provided as was preparation for receiving psilocybin. A target quit date was set to occur with the first dosage of psilocybin during week five, when the subjects were given 20 mg/70 kg of psilocybin. Weekly meetings continued, and then on the seventh week, a higher dose of 30 mg/70 kg was given. During the 13th week, the higher dose of psilocybin was made optional for the subjects. Before the psilocybin was administered, subjects noted their motivational statement for smoking cessation. The subjects also participated in a guided imagery exercise at the end of the first psilocybin session [91]. At six-month follow-up, 80% of the former smokers (12 of 15) were abstinent from tobacco, as verified by breath and urine tests. This was a much higher abstinence rate than seen with traditional smoking cessation programs [91].

The researchers returned to their subjects later, reporting on smoking abstinence at 12 months and over the long term, with an average of 30 months after the study. They found that at the 12-month point, 67% were abstinent from smoking. At the long-term point, 60% were still smoking-abstinent, an excellent success rate [92].

In an older study of single versus repeated sessions of ketamine-assisted psychotherapy in 59 subjects who had detoxified from heroin, subjects were divided into two groups. The subjects in the first group received two addiction counseling sessions with ketamine, followed by two ketamine-assisted psychotherapy sessions, with sessions held at monthly intervals. The subjects in the second group received two addiction counseling sessions without ketamine and one ketamine therapy session. At the one-year follow-up point, 50% of subjects in the first group were still abstinent from heroin, versus 22.2% of subjects in the second group. The researchers concluded that three sessions in the ketamine-assisted psychotherapy program was more effective in promoting abstinence from heroin than one session followed by counseling [93]. There are also emerging data showing positive effects in alcohol use disorders and other substance use disorders.

It is important to keep in mind comparable efficacy. For opioid use disorder, it is vital to know both short- and long-term safety and efficacy comparisons to the standard of care (medication-assisted treatment plus therapy). Also consider that psychedelics will not be proved safe and effective by a professional consensus but rather by the FDA. It may be that psychoactive substances are legalized much in the same fashion cannabis has, but whether they are approved for clinical use will depend on the outcomes of Phase 2 and 3 FDA-qualifying clinical trials and safety and comparable efficacy trials. As of 2022, these trials are ongoing.

## ANXIETY AND DEPRESSION RELATED TO LIFE-THREATENING DIAGNOSES

As discussed, research has demonstrated that psilocybin can be effective in improving mood and quality of life of patients with terminal cancer diagnoses. This aspect of cancer care has been largely overlooked and undertreated. Agrawal notes that, "Oncologists are well-equipped to fight the physical threats of cancer with powerful, yet sometimes imperfect tools including chemotherapy, radiation, and surgery, but they often feel helpless when it comes to treating the intense psychological agony many patients experience" [94]. A seminal study published in 2016 explored the use of a modest dose of psilocybin given to patients with terminal cancer under the supervision of trained therapists. The findings demonstrated that more than 80% of 51 patients who had received life-threatening cancer diagnoses and who subsequently developed depression or anxiety experienced significant and sustained improvements in mood and quality of life six months after taking psilocybin. In addition to feeling calmer and happier, the participants reported forging a closer connection with their friends and family [95]. This study demonstrated the careful and controlled use of psilocybin might be a safe and effective treatment for existential anxiety and despair that often accompany advanced-stage cancers. In addition, in limited studies, LSD has been found to significantly decrease anxiety levels in patients with life-threatening diseases.

Oncology and palliative care specialties have been associated with relatively high burnout rates, at least in part from seeing the psychological distress of patients with potentially terminal diagnoses. In this setting, any therapy that can improve patients' experiences and mood would be beneficial, and initial results of research incorporating psilocybin, LSD, and other psychedelics has been positive [94]. Agrawal further states [94]:

> I have never witnessed the sort of dramatic response to any medical intervention as I have with some patients through psychedelic-assisted therapy. It is not a magic bullet or cure for a cancer patient's suffering—and it won't change their prognosis or life expectancy. But it could be a spark that begins their healing journey, helping them come to terms with their most difficult fears.

The use of psychedelic medications in end-of-life care is logical and should be tested compared to the standard treatment (counseling) in randomized, blind clinical trials and other investigations to facilitate FDA approval.

## OBSESSIVE-COMPULSIVE DISORDER

OCD can be an extremely debilitating disorder that is often difficult to treat. In a 2006 study of nine subjects with treatment-resistant OCD who were treated with psilocybin, the subjects experienced a significant decrease (range 23% to 100%) in OCD symptoms. One of the subjects experienced an issue with temporary hypertension. These are positive findings; however, it is obviously a very small study and additional research would be needed to replicate findings in a larger and more diverse group [96].

Other researchers have discussed the potential for the use of ketamine and esketamine in treating OCD [97]. In a 2013 randomized, double-blind, placebo-controlled, crossover study of drug-free adults with OCD, subjects were given two 40-minute intravenous infusions, one of saline and one of ketamine (0.5 mg/kg), spaced at least one week apart [98]. Individuals who received ketamine reported significant improvement in obsessions (measured by OCD visual analog scale) during the infusion compared with those given placebo. One-week post-infusion, 50% of those who had received ketamine met the criteria for treatment response (defined as a 35% or greater reduction in Yale-Brown Obsessive-Compulsive Scale scores); no subjects receiving placebo displayed treatment response after one week. The authors of this study concluded that "rapid anti-OCD effects from a single intravenous dose of ketamine can persist for at least one week in some patients with constant intrusive thoughts" [98]. However, other studies have found no effect on OCD symptoms [99]. Solid evidence is lacking and requires greater and more rigorous research.

### SOCIAL ANXIETY IN PATIENTS WITH AUTISM

In a study of 12 adults with autism and issues with severe social anxiety, subjects were randomized to receive either MDMA (75 mg or 125 mg) or placebo during the course of two 8-hour psychotherapy sessions. The MDMA was administered after a guided progressive muscle relaxation exercise. The experimental sessions were held one month apart and separated by three nondrug sessions of psychotherapy. The patients were provided with as few sensory interruptions as possible, such as soft lights, noise abatement, and fidget objects to help them with self-regulation through repeated actions (i.e., "stimming") [100]. On the Leibowitz Social Anxiety Scale, the MDMA group experienced a significantly greater improvement in social anxiety scores compared with the placebo group. Improvements persisted at six-month follow-up. The researchers said of the follow-up, "social anxiety remained the same or continued to improve slightly for most participants in the MDMA group after completing the active treatment phase" [100].

Social anxiety disorder is relatively common among the general population; about 12% suffer from this disorder at some point in their lives [101]. If it is determined to be an effective treatment, MDMA-assisted psychotherapy could be an option for these patients who have not responded to traditional psychotherapy or pharmacotherapy.

### ANOREXIA NERVOSA

Anorexia nervosa is a severe eating disorder characterized by restriction of energy intake relative to an individual's requirements, typically resulting in low body weight and malnutrition. It is notoriously difficult to treat and has a high mortality rate. Experts have continued to search for more effective treatment options for this population.

In one study, the authors treated 15 patients (23 to 42 years of age) with treatment-resistant anorexia nervosa with infusions of 20 mg/hour of ketamine over 10 hours. The subjects were also given 20 mg twice per day of nalmefene. The subjects showed a marked decreased in scores on compulsion. Before the ketamine was administered, the average scores were 44.0; after treatment, mean compulsion scores dropped to 27.0. Nine of the subjects (60%) showed remission after two to nine ketamine infusions over the course of five days to three weeks [102]. The authors reported the following details on three specific patients [102]:

> Patient 4 increased her weight after three treatments but agreed to more in the hope that her compulsion score would come down further. After a year in follow-up with a normal weight, she then started work and remained in a stable state while followed-up for nine months.
>
> Patient 5 was a married woman and reached a normal weight after five treatments. As an outpatient, her periods returned and she had a successful pregnancy. Patient 6 had a long history of alternating anorexia and bulimia. After four treatments and despite only a small fall in compulsion score, she became able to control her eating and her weight. She held a responsible job with no relapse during two years of follow-up.

In a 2020 study with only one subject, the researchers treated a patient, 29 years of age, who had developed anorexia nervosa at 14.5 years of age and had been unable to attain remission. The researchers prescribed a ketogenic diet along with intravenous ketamine infusions. (A ketogenic diet was chosen because it had proven in the past to prevent starvation, a real risk with anorexia.) The patient sustained complete recovery and continued her ketogenic diet while maintaining a normal weight [103]. After three months, the woman remained on the ketogenic diet and reported feeling significantly better but still suffered from anorexic compulsions. At that time, she was sent for ketamine infusions. The patient reported that within one hour of her first infusion the "anorexic voice" inside her was decreasing and she felt more like herself. The patient had three more infusions over the next 14 days. After the fourth infusion, the patient stated [103]:

> I know this sounds ridiculous, but I am no longer anorexic. I had so many rules I didn't even know them. But they are gone. I can exercise because it feels good. It isn't that I have to. I can stop when I want to.

Because this study had two potentially essential factors (ketamine and the ketogenic diet), it is unclear if either or both are responsible for the single patient's improvements. As is the case for many of these novel treatments, additional research is warranted.

### CLUSTER HEADACHES

Cluster headaches, which affect less than 1% of adults, are considered to be the most painful of all headaches and can last for a week or longer, potentially becoming a chronic health issue [104]. Traditional treatment approaches include triptan medications and oxygen therapy. Understandably, most sufferers seek quick relief and would prefer to never experience another attack.

In one report, the authors interviewed 53 people with cluster headaches who had self-medicated with psilocybin or LSD. (This is not recommended or considered safe.) Of 26 patients who used psilocybin, 22 said the drug successfully aborted their headache attacks. Of five people who said they used LSD to treat their headaches, four reported experiencing remission [105]. Based on these findings, the authors recommend further study of psychedelics as a possible treatment for cluster

headaches. It is important to remember that self-reports are no basis for concluding that psilocybin or LSD is effective at improving a cluster headache condition. There is a current clinical trial underway examining the role of LSD as a possible treatment for cluster headaches [106].

In another study of 77 patients with treatment-resistant migraines or new daily headaches, all of whom had failed aggressive outpatient and inpatient treatment, patients were infused with ketamine. According to the researchers, the mean headache pain rating at the start of the study was 7.1; this fell to 3.8 upon discharge. Most of the patients responded well to the ketamine. Researchers concluded [107]:

> Pending higher level evidence and given that ketamine is generally well-tolerated, ketamine may be considered a reasonable acute treatment for well-selected headache patients for whom standard therapies are either ineffective or medically contraindicated.

### OTHER DISORDERS

Some psychiatric disorders, particularly those with psychotic features such as schizophrenia, schizophreniform disorder, brief psychotic disorder, schizoaffective disorder, and delusional disorder, should certainly not be treated with psychedelic drugs. It is unclear if other psychiatric conditions would be amenable to psychedelic treatment. This can only be determined by clinical trials that administer these drugs under scientific rigor and with a sufficiently high number of patients. Many of the studies published to date have included very small numbers of patients, though this is largely because of necessity. It may have been that few individuals with the disorder could be recruited into a trial consisting of experimental treatment with a psychedelic drug. As the knowledge base grows based on clinical trials, it is hoped that it will become increasingly more feasible to test psychedelics on patients with a multitude of psychiatric disorders, particularly for those individuals whose conditions have been challenging to treat.

## INTERVENTIONAL PSYCHIATRY: BRAIN STIMULATION THERAPIES

Electroconvulsive therapy has been in use for nearly a century and continues to be used in psychiatric treatment today. Newer forms of brain stimulation are increasing popular options for patients—or likely will be soon at major medical centers, including rTMS, VNS, and DBS. New brain mapping techniques may help eliminate the need for more invasive procedures. Interventional psychiatry represents an opportunity to help patients who otherwise have found no relief from pharmacotherapy and standard treatments [108].

For health professionals interested in the latest techniques on neuromodulation to aid patients with refractory psychiatric disorders, interventional psychiatry may be the answer. In order for physicians to effectively enter this field, experts recommend an additional year of training with an emphasis on interventional psychiatry.

### ELECTROCONVULSIVE THERAPY

ECT has been used to treat depression, bipolar disorder, schizophrenia, and other psychiatric diagnoses for many years, starting in the first half of the 20th century. The goal of ECT is to induce a seizure through applied electric shocks. The procedure was initially introduced in the late 1930s in Italy, and in the 1940s through the 1960s, ECT became popular in the United States as a mainstream treatment [109]. However, early treatments did not provide anesthesia and sometimes led to physical and psychological trauma [110]. Physicians later learned that significantly milder shocks could achieve the same goals.

Today, the procedure is used rarely for treatment-resistant depression and major depression with suicidal ideation or behaviors, as well as for schizophrenia and schizoaffective disorder. A team of professionals are involved, including a psychiatrist, a neurologist, an anesthesiologist, and a nurse [110]. Some believe that ECT should be used before psychedelics or newer brain intervention therapies are attempted, although agreement on this subject is not universal. It should also be noted that there is some residual fear/concern of ECT itself that persists among many patients (and some healthcare professionals), largely because ECT was historically traumatic. However, ECT has proven highly effective at treating both major depressive disorder and suicidal depression. About 100,000 patients receive ECT each year, and most of them are residents in psychiatric hospitals or psychiatric units of hospitals [111].


The National Institute for Health and Care Excellence recommends clinicians consider electroconvulsive therapy (ECT) for the treatment of severe depression if the person chooses ECT in preference to other treatments based on their past experience of ECT and what has previously worked for them OR a rapid response is needed (e.g., if the depression is life-threatening) OR other treatments have been unsuccessful.

(https://www.nice.org.uk/guidance/ng222. Last accessed July 8, 2022.)

**Level of Evidence**: Expert Opinion/Consensus Statement

The modern use of ECT consists of [112]:

> induction of brief general anesthesia (typically lasting less than 10 minutes), pharmacologic muscle relaxation, and continuous monitoring of oxygen saturation, blood pressure, and heart rate, and rhythm. An electrical charge is delivered to the brain through scalp electrodes, which results in a generalized seizure typically lasting for 20 to 60 seconds. Most patients receive between 6 and 12 treatments spaced over a period of 2 to 4 weeks as an initial course of treatment.

Patients who receive ECT may have mild-to-moderate cognitive side effects that generally resolve within days or weeks after the course of treatment has ended [112]. Improvement in depressive symptoms is apparent as soon as the third treatment, and remission rates may be as high as 60% among patients with treatment-resistant depression [113].

In a study of 31 patients with major depressive disorder who received ECT treatment, neurocognitive function was assessed with multiple tests, such as the MATRICS Consensus Cognitive Battery, the Everyday Memory Questionnaire, and the MADRS. These instruments were used before ECT, six weeks after ECT, and six months after the procedure. There was a significant decrease in depression scores six weeks and six months after ECT. Patients also exhibited significantly improved neurocognitive abilities six weeks subsequent to the ECT; these improvements were maintained at six months. The researchers concluded that improvements in depression and stability of subjectively reported memory function indicate that the antidepressant effects of ECT do not occur at the expense of cognitive function [114].

A Swedish analysis of 254,906 sessions of ECT conducted with 16,681 individuals between 2012 and 2019 found that fewer than 1% of individuals suffered broken teeth incurred as a result of their treatment. More specifically, the rate was 0.3% per individual, and there were no differences found between patients by age, gender, or diagnosis, although the dental fracture group had a greater number of treatments. Despite the low rate, bite guards and muscle relaxants are recommended to be used as a safety precaution during treatment with ECT [115].

In a 2021 survey of 192 ECT physician practitioners in the United States, 30% of the survey respondents had graduated from one of 12 residency programs in the United States. Several barriers to ECT programs were identified, stigma against ECT on the part of patients and problems with patient transportation, because patients cannot drive themselves home after treatment [116]. With regard to starting a new ECT program, barriers included lack of well-trained ECT practitioners, lack of institutional support or interest in leading the initiative, and insufficient physical space at the facility. The highest concentration of ECT providers were based in New England, and the lowest concentration was in the southern central region of the United States. Overall, the researchers were able to identify a variety of institution-related barriers (e.g., finances, bureaucracy, stigma, lack of understanding) that prevent enthusiastic adoption of this intervention. As a result, although ECT potentially could provide relief to many patients with treatment-resistant depression and other disorders, it may not be an option for many patients who live remotely from centers that offer this service.

In a 2018 study, a MarketScan database of more than 47 million patients was analyzed to determine the incidence of ECT. Of about 1 million patients with a mood disorder, 2,471 (0.25%) had received ECT. Individuals who had received ECT were five times more likely to have additional comorbid psychiatric disorders and twice as likely to have comorbid substance use disorder [117]. Whether ECT should be used more frequently is beyond the scope of this course, but it is important to understand that is can be an effective treatment even though it remains rarely used.

**TRANSCRANIAL MAGNETIC STIMULATION (TMS)**

TMS, a noninvasive form of neural modulation, was initially developed in the 1980s. Later, it was discovered that repeated sessions of TMS (rTMS) were more effective than a single treatment. In 2008, the FDA approved rTMS to treat major depressive disorder; in 2018, it was approved to treat OCD [118]. Trials are also investigating the efficacy of rTMS in the treatment of substance use disorders with alcohol, opioids, cannabis, tobacco, methamphetamine, and cocaine [119]. The procedure is also used to treat patients with neurologic disorders, including Parkinson disease, multiple sclerosis, and stroke [120].

An increasingly popular procedure in the United States and other Western countries, rTMS is available at major medical centers throughout the country. This procedure uses large magnets to stimulate the neurons in the prefrontal cortex of the brain. An electromagnetic coil is placed on the patient's forehead at the site of the left prefrontal cortex, an area of the brain that often displays reduced activity in persons with severe and refractory depression. Nonpainful electromagnetic pulses pass through the skin and to the brain. There is no anesthesia needed or given with this procedure, and the only potential adverse effects are headache and minor discomfort in the scalp.

In a U.S. study involving 247 adults with severe treatment-resistant depression, the efficacy of rTMS in improving psychiatric symptoms was evaluated. The average age of the subjects was 43 years, and the average Patient Health Questionnaire-9 score was 21.7. The subjects received single 37-minute sessions over six weeks, up to a maximum of 30 total sessions [121]. Following rTMS therapy, there was a remission rate of 72%

after three weeks, with no differences in response by sex of the subject, but age was a factor, with older individuals taking a longer time to achieve remission of their depression. In addition, remission correlated with past suicide attempts, previous psychiatric hospitalizations, and substance use disorder, illustrating that the procedure was highly effective for individuals with severe and/or comorbid disease. In this study, there was a higher efficacy with the MagVenture device compared with the NeuroStar device.

A Dutch study randomized 14 patients with alcohol use disorder to 10 days of rTMS therapy and 16 patients to sham rTMS. The patients were subsequently evaluated for alcohol craving and alcohol use. For a period of time, subjects in the rTMS treatment group reported lower levels of alcohol craving and use than those in the control group. Differences in alcohol craving in the study group were most prevalent 3 months after treatment; at the 12-month point, there were no differences between the two groups, indicating the beneficial effects of rTMS may fade over time [122].

Because rTMS is a safe and effective FDA-approved treatment for depression, some experts have recommended turning the treatment algorithm for depression upside down, putting TMS in a first-choice position. Rather than requiring patients to undergo months of potentially ineffective antidepressant trials, starting with TMS (with an artificial intelligence component to ensure the right dose and optimal targeting) may be a better option [123]. Additional studies are underway to examine TMS and expand evidence-based access to this treatment [123].

Another form of TMS, Stanford accelerated intelligent neuromodulation therapy (also known as Stanford neuromodulation therapy or SAINT), has been associated with an extremely high success rate in patients with treatment-resistant depression. In a 2022 study, nearly 80% of 29 subjects who had been depressed for a mean period of nine years experienced remission in just four weeks. This is a much quicker response time than traditional antidepressant therapy. The difference between SAINT and other TMS procedures lay with a greater number of treatments for a shorter time frame, such as 10-minute sessions 10 times per day. These treatments are also more targeted to the patient's brain circuitry [124].

## VAGUS NERVE STIMULATION

VNS is an invasive form of neuromodulation consisting of implantation of a device that sends electrical pulses to the vagus nerve of the brain. The vagus nerve (also referred to as cranial nerve X) is very long and extends from the brain into the neck, chest, and abdomen. This nerve has many effects and impacts such diverse functions as mood, digestion, blood pressure, heart rate, immune function, saliva production, and taste [125].

The first VNS event occurred in the 1880s in New York, when James Corning applied an electrical current to a carotid compression fork, believing this approach would prevent or end seizures [126]. The procedure has evolved drastically to become the sophisticated procedure used today.

In 2005, the FDA approved VNS for the management of treatment-resistant depression [127]. Since then, a transcutaneous form of VNS has been developed, eliminating the need for surgery. However, this approach was not approved by the FDA as of 2022.

Some researchers have noted that cognitive dysfunction may accompany depression and be a factor in the associated reduced work productivity. A Canadian study analyzed the cognitive performance of individuals with treatment-resistant depression subsequent to their treatment with VNS. In 14 subjects, both the learning capabilities and memory of the subjects improved significantly after one month of receiving VNS. These cognitive improvements persisted for years subsequent to treatment with VNS. After VNS, 29% of the subjects experienced remission from treatment-resistant depression after 1 month, 50% after 3 months, 57% at 12 months, and 64% at 24 months. As such, at the end of the study, nearly two-thirds of patients had recovered with VNS therapy [128]. The researchers stated [128]:

> Improvements were observed in measures of psychomotor speed, verbal fluency, attention, and executive functioning, as well as verbal and visual memory. We observed clear differences in improvement rate between cognitive measure. Memory measures, such as recall of a complex figure, as well as learning and recall of a word list, show more than 25% improvement after two months of treatment.

## DEEP BRAIN STIMULATION THERAPIES

An invasive form of therapy that is used infrequently, DBS has proven effective at treating severe depression and OCD. DBS is also approved to treat some patients with severe, refractory neurologic disorders, such as epilepsy and Parkinson disease. DBS is also under investigation for the treatment of schizophrenia, Alzheimer disease, substance use disorder, and other challenging psychiatric disorders [129].

The first documented use of DBS occurred in 1948, when neurosurgeon J. Lawrence Pool implanted an electrode into the brain of a women with anorexia and depression. Results were initially positive, until the wire broke several weeks later [130]. Today, DBS involves the permanent implantation of electrodes that send regular and continuous electrical impulses to stimulate a specific part of the brain. Some describe DBS as a sort of brain pacemaker to correct imbalances, comparable to a heart pacemaker that corrects cardiac abnormalities. It should be noted that DBS is an invasive and expensive procedure that is only available to very few individuals, and it is not approved for the treatment of depression by the FDA as of 2022.

The electrodes used in DBS are made of platinum-iridium wires and nickel alloy connectors, which are enclosed in a polyurethane sheath [129]. Some patients may worry about the potential for hacking into a DBS system in today's connected world and the possibility of control over individuals, referred to as "brainjacking." This does not appear to be a problem at this time of very limited use of DBS, but it is a subject worthy of consideration in the future.

In a nationwide database of 116,890 hospitalized patients in the United States with major depressive disorder, patients receiving DBS represented 0.03% [131]. The average age of participants was 49.1 years; all were White, and 88% were female. Patients stayed in the hospital for 1 to 1.6 days. The highest rate of DBS use occurred in the southern United States, followed by the northeast and west. Patients receiving DBS either had private insurance or they were self-pay patients [131].

In a study of five patients with severe OCD who received DBS over the period 2015–2019, not only did the patients experience improvement in their OCD symptoms after DBS, but they also experienced a 53% improvement in their levels of depression (on the MADRS scale) and a 34.9% improvement on the Hamilton Anxiety Rating scales. In addition, patients also improved on the Quality of Life Enjoyment and Satisfaction Questionnaire [132]. The researchers reported anecdotal evidence of improvement as well, such as this report from one of the five patients [132]:

> Despite persistent low body mass index [BMI] of 14, she has remained out of the hospital for 29 months, the longest time period since onset of OCD and anorexia. She is working part-time as a research assistant, is active in her church, and though she wishes for further reduction in symptoms, she notes her quality of life and mood is better than prior to DBS. In addition, she no longer engages in self-injurious behaviors and no longer experiences suicidal ideation.

In another study, DBS was used to treat seven patients with treatment-resistant depression [133]. Researchers specifically targeted the bilateral habenula, which is the seat of the anti-reward system [133]. After one month, depression and anxiety symptoms had decreased by 49%, and the patients reported a dramatic improvement in their quality of life.

In a one-person study of an individual treated with DBS for treatment-resistant depression, the patient experienced continuous improvement until depressive symptoms remitted by the 22nd week. At 37 weeks, the subject was randomized to continuous treatment or discontinuation. When treatment was stopped, the patient reported increasingly worse depression and anxiety until he met rescue criteria, resulting in the resumption of treatment. The depression symptoms rapidly abated when treatment restarted [134].

## CAUTIONS

Although the news about both psychedelics and brain stimulation techniques is generally positive, caution is important, particularly in the case of psychedelic drugs. Patients should be actively discouraged from trying psychedelic drugs on their own, because these drugs can trigger an underlying psychosis in individuals who would otherwise likely have remained healthy, particularly because dosage and purity of the illicit drug is unpredictable. In addition, FDA-approval processes, regulated pharmaceutical drugs rather than street drugs, and comparable efficacy can help identify the safest and most effective medication or interventional treatment for a particular patient at a particular time. In essence, buying MDMA and taking it is not the same as being administered MDMA in a PTSD clinical trial at a research institution. Today, adulteration of street drugs is of great concern, particularly with potentially lethal doses of fentanyl [135].

Patients have no idea what dosage is in a street drug and could take a suboptimal dose (to no effect) or take an excessively high dose of the drug, which could cause inadvertent harm. Importantly, patients under the influence of such drugs require supervision, lest they take actions that might be potentially dangerous to themselves or others.

For patients considered for psychedelic or interventional psychiatric options who are not proficient in English, it is important that information regarding the risks associated with the use of psychedelics and/or interventional procedures 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.

## CONCLUSION

It is apparent that psychedelic medicine is now in a renaissance period, and this time could not have come too soon. Many people in the United States and around the world suffer from severe psychiatric disorders, including depression, PTSD, substance use disorders, anxiety disorders, OCD, anorexia nervosa, and multiple other psychiatric disorders that are not readily responsive to treatment with pharmacotherapy and/or psychotherapy [136]. In the aftermath of the COVID-19 pandemic, depressive disorders are more prevalent, and people are urgently and actively seeking effective treatments. Exploration of novel interventional and psychedelic therapies may be a path to recovery for patients with mental health disorders who have not improved on traditional approaches [137].

## FACULTY BIOGRAPHY

**Mark S. Gold, MD, DFASAM, DLFAPA**, is a teacher of the year, translational researcher, author, mentor, and inventor best known for his work on the brain systems underlying the effects of opiate drugs, cocaine, and food. Dr. Gold was a Professor, Eminent Scholar, Distinguished Professor, Distinguished Alumni Professor, Chairman, and Emeritus Eminent Scholar during his 25 years at the University of Florida. He was a Founding Director of the McKnight Brain Institute and a pioneering neuroscience-addiction researcher funded by the NIH-NIDA-Pharma, whose work helped to de-stigmatize addictions and mainstream addiction education and treatment. He also developed and taught courses and training programs at the University of Florida for undergraduates and medical students. He continues on the Faculty of the University of Florida, Tulane, and Washington University in St Louis.

He is an author and inventor who has published more than 1,000 peer-reviewed scientific articles, 20 text books, popular-general audience books, and physician practice guidelines. Dr. Gold was co-inventor of the use of clonidine in opioid withdrawal and the dopamine hypothesis for cocaine addiction and anhedonia. Both revolutionized how neuroscientists and physicians thought about drugs of abuse, addiction, and the brain. He pioneered the use of clonidine and lofexidine, which became the first non-opioid medication-assisted therapies. His first academic appointment was at Yale University School of Medicine in 1978. Working with Dr. Herb Kleber, he advanced his noradrenergic hyperactivity theory of opioid withdrawal and the use of clonidine and lofexidine to ameliorate these signs and symptoms. During this time, Dr. Gold and Dr. Kleber also worked on rapid detoxification with naloxone and induction on to naltrexone.

Dr. Gold has been awarded many state and national awards for research and service over his long career. He has been awarded major national awards for his neuroscience research including the annual Foundations Fund Prize for the most important research in Psychiatry, the DEA 30 Years of Service Pin (2014), the American Foundation for Addiction Research's Lifetime Achievement Award (2014), the McGovern Award for Lifetime Achievement (2015) for the most important contributions to the understanding and treatment of addiction, the National Leadership Award (NAATP) from addiction treatment providers for helping understand that addiction is a disease of the brain, the DARE Lifetime Achievement Award for volunteer and prevention efforts, the Silver Anvil from the PR Society of America for anti-drug prevention ads, the PRIDE and DARE awards for his career in research and prevention (2015), and the PATH Foundation's Lifetime Achievement Award (2016) as one of the "fathers" of addiction medicine and MAT presented to him by President Obama's White House Drug Czar Michael Botticelli. He was awarded Distinguished Alumni Awards at Yale University, the University of Florida, and Washington University and the Wall of Fame at the University of Florida College of Medicine. Gold was appointed by the University President to two terms as the University's overall Distinguished Professor, allowing him to mentor students and faculty from every college and institute. The University of Florida College of Medicine's White Coat Ceremony for new medical students is named in his honor.

Since his retirement as a full-time academic in 2014, Dr. Gold has continued his teaching, mentoring, research, and writing as an Adjunct Professor in the Department of Psychiatry at Washington University and an active member of the Clinical Council at the Washington University School of Medicine's Public Health Institute. He regularly lectures at medical schools and grand rounds around the country and at international and national scientific meetings on his career and on bench-to-bedside science in eating disorders, psychiatry, obesity, and addictions. He continues on the Faculty at the University of Florida College of Medicine, Department of Psychiatry as an Emeritus Distinguished Professor. He has traveled extensively to help many states develop prevention, education, and treatment approaches to the opioid crisis.

**Customer Information/Answer Sheet/Evaluation insert located between pages 56–57.**

## COURSE TEST - #96790 PSYCHEDELIC MEDICINE AND INTERVENTIONAL PSYCHIATRY

*This is an open book test. Please record your responses on the Answer Sheet.*
*A passing grade of at least 70% must be achieved in order to receive credit for this course.*

*In accordance with the AMA PRA Category 1 Credit™ system,*
*physicians must complete and pass a post-test to receive credit.*

***This 10 credit activity must be completed by June 30, 2025.***

**1. Which of the following is a category of psychedelic drugs?**
- A) *Classic*
- B) *Natural*
- C) *Prescription*
- D) *Hallucinogenic*

**2. Psilocybin has been legalized for consumer use in**
- A) *Oregon.*
- B) *California.*
- C) *New York.*
- D) *New Mexico.*

**3. A hallucinogen is**
- A) *an illicit drug of abuse in all cases.*
- B) *any substance that allows for intensified experiences.*
- C) *a drug that is used to facilitate guided imagery exercises.*
- D) *any drug that may cause the user to experience visual, auditory, or other types of hallucinations.*

**4. In the context of psychedelic medicine, set refers to**
- A) *the patient's mindset.*
- B) *the process of providing effective therapy.*
- C) *the environment in which therapy is provided.*
- D) *the manual of best practices established for therapy.*

**5. Ketamine is considered a**
- A) *Schedule I drug.*
- B) *Schedule II drug.*
- C) *Schedule III drug.*
- D) *non-scheduled drug.*

**6. In the 1940s, LSD was marketed under the brand name Delysid for the treatment of**
- A) *neurosis.*
- B) *alcoholism.*
- C) *schizophrenia.*
- D) *All of the above*

**7. Patients who receive psychedelic therapy experience better outcomes if the therapy is administered in settings in which**
- A) *they feel safe.*
- B) *they are completely alone.*
- C) *everything is new or unfamiliar.*
- D) *hallucinogenic effects are promoted by loud music and flashing colors.*

**8. Which of the following is an aspect of psychedelic medicine setting that can enhance set?**
- A) *Music*
- B) *Lighting*
- C) *Presence of a supportive healthcare professional*
- D) *All of the above*

**9. Which of the following statements regarding psilocybin is FALSE?**
- A) *The duration of action is four to six hours.*
- B) *It is active orally at doses of around 10 mg.*
- C) *Time to onset of effect is usually within 20 to 30 minutes of ingestion.*
- D) *It is about 20 times stronger than LSD but much less potent than mescaline.*

**10. Nasal spray esketamine is approved by the FDA for the treatment of**
- A) *schizophrenia.*
- B) *cluster headaches.*
- C) *opioid use disorder.*
- D) *treatment-resistant and/or suicidal depression.*

*Test questions continue on next page* ➞

**11. Researchers have demonstrated the efficacy of combination psychotherapy and MDMA in the treatment of**
- A) *PTSD.*
- B) *depression.*
- C) *end-of-life anxiety.*
- D) *obsessive-compulsive disorder.*

**12. Which of the following statements regarding ibogaine is TRUE?**
- A) *It is a derivative of phencyclidine (PCP).*
- B) *It is FDA-approved for the treatment of opioid use disorder.*
- C) *Its metabolism is purportedly mediated by the p450 cytochrome enzyme CY2D6.*
- D) *It is easiest to obtain in the United States, and travel from other countries to obtain treatment is common.*

**13. Which of the following statements regarding kratom products in the United States is TRUE?**
- A) *All kratom products are considered Schedule I drugs.*
- B) *The products are typically freeze-dried leaves, concentrated extracts, or liquid "energy shots."*
- C) *Products marketed in the United States have been tested for purity and uniform concentration.*
- D) *While kratom products are available locally in smoke and "head" shops, they cannot be legally purchased over the Internet.*

**14. Mescaline toxicity can result in**
- A) *bradycardia.*
- B) *hypotension.*
- C) *hypothermia.*
- D) *respiratory depression.*

**15. Nitrous oxide has been demonstrated to improve the condition of individuals with**
- A) *PTSD.*
- B) *psychosis.*
- C) *treatment-resistant depression.*
- D) *attention deficit Hyperactivity disorder.*

**16. The most common adverse effect of ayahuasca is**
- A) *flashbacks.*
- B) *severe headache.*
- C) *nausea and vomiting.*
- D) *respiratory depression.*

**17. Research indicates that a modest dose of psilocybin given to patients with terminal cancer under the supervision of trained therapists can improve**
- A) *prognosis.*
- B) *life expectancy.*
- C) *mood and quality of life.*
- D) *tumor size and associated pain.*

**18. Which of the following psychedelics has been studied for the treatment of social anxiety in persons with autism?**
- A) *MDMA*
- B) *Ibogaine*
- C) *Mescaline*
- D) *Psilocybin*

**19. The goal of electroconvulsive therapy (ECT) is to**
- A) *stimulate the prefrontal cortex.*
- B) *provide a competing traumatic experience.*
- C) *induce a seizure through applied electric shocks.*
- D) *induce the creation of new dendrites in the brain.*

**20. Deep brain stimulation**
- A) *is dangerous and potentially painful.*
- B) *is the subject of intense research for the treatment of eating disorders.*
- C) *has been proven effective in amelioration of severe depression in large randomized controlled trials.*
- D) *involves the permanent implantation of electrodes that send regular and continuous electrical impulses to stimulate a specific part of the brain.*

Be sure to transfer your answers to the Answer Sheet insert located between pages 56–57.
***PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.***

# Pharmacologic and Medical Advances in Obesity Management

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

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

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

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

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

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

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

***Division Planner***
John M. Leonard, MD

***Senior Director of Development and Academic Affairs***
Sarah Campbell

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

### *Accreditations & Approvals*

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### *Designations of Credit*

NetCE designates this enduring material for a maximum of 15 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 15 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

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

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

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 15 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

This activity has been designated for 15 Lifelong Learning (Part II) credits for the American Board of Pathology Continuing Certification Program.

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

### *Special Approvals*

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- Read the following course.
- Complete the test questions at the end of the course.
- Return your Customer Information/Answer Sheet/Evaluation and payment to NetCE by mail or fax, or complete online at **www.NetCE.com/MD24**.
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Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the study questions and course material for better application to your daily practice.

  

## INTRODUCTION

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

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

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

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

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

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

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

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

## DEFINITIONS OF OBESITY

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

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

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

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

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

| 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* |

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

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

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

## CLINICAL ASSESSMENT

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

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

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

  

The AMA policy recognizes that [35]:

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

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

## EPIDEMIOLOGY

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

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

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

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

### POPULATION PREVALENCE

#### Adults 20 Years of Age and Older

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

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

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

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

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

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

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

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

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].

| PREVALENCE OF OBESITY AND SEVERE OBESITY AMONG ADULTS AGED 20–74 YEARS | | | | | | |
|---|---|---|---|---|---|---|
| **Year** | **Percent of Population Considered Obese (BMI ≥30 kg/m²)** | | | **Percent of Population Considered Severely Obese (BMI ≥40 kg/m²)** | | |
| | **Total** | **Male** | **Female** | **Total** | **Male** | **Female** |
| 1960–1962 | 13.4% | 10.7% | 15.8% | 0.9% | 0.3% | 1.4% |
| 1971–1974 | 14.5% | 12.1% | 16.6% | 1.3% | 0.6% | 2.0% |
| 1976–1980 | 15.0% | 12.7% | 17.0% | 1.4% | 0.4% | 2.2% |
| 1988–1994 | 23.2% | 20.5% | 25.9% | 3.0% | 1.8% | 4.1% |
| 1999–2000 | 30.9% | 27.7% | 34.0% | 5.0% | 3.3% | 6.6% |
| 2001 | 31.2% | 28.3% | 34.1% | 5.4% | 3.9% | 6.8% |
| 2003 | 32.9% | 31.7% | 34.0% | 5.1% | 3.0% | 7.3% |
| 2005 | 35.1% | 33.8% | 36.3% | 6.2% | 4.3% | 7.9% |
| 2007 | 34.3% | 32.5% | 36.2% | 6.0% | 4.4% | 7.6% |
| 2009 | 36.1% | 35.9% | 36.1% | 6.6% | 4.6% | 8.5% |
| 2011 | 35.3% | 33.9% | 36.6% | 6.6% | 4.5% | 8.6% |
| 2013 | 38.2% | 35.5% | 41.0% | 8.1% | 5.7% | 10.5% |
| 2015 | 40.0% | 38.3% | 41.6% | 8.0% | 5.9% | 10.1% |
| 2017–2018 | 42.8% | 43.5% | 42.1% | 9.6% | 7.3% | 12.0% |

*Source: [41]* *Table 2*

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.

  

| 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*

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

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

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

## PERSONAL AND SOCIETAL BURDEN OF OBESITY

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

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

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

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

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

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

## MORTALITY

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

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

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

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

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

  

| 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* |

## ETIOLOGY OF THE OBESITY EPIDEMIC

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

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

### DIET, PHYSICAL ACTIVITY, AND BMI

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

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

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

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

**Macronutrient Intake and BMI: 1965–2011**

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

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

**Dietary Changes: 1999–2016**

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

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

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

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

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

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

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

**Weight Loss Attempts: 1999–2016**

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

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

## ENERGY EXPENDITURE RESEARCH

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

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

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

  

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

**Additive versus Constrained Models of Metabolic Physiology**

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

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

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

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

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

**Energy Compensation**

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

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

**Resting Energy Expenditure in Healthy Underweight Adults**

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

**Declining Metabolic Rate and Rising Obesity**

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

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

In addition, the reduction in total energy expenditure was linked to a decline in basal energy expenditure. Declining basal energy expenditure is less easily understood, but consistent with data that body temperatures also declined over the same period as decreasing basal metabolic rate. The magnitude of change in basal metabolic rate is consistent with studies showing that basal metabolic rate increases 10% to 25% with every 1°C increase in core temperature [80]. The authors conclude

that a declining basal metabolic rate may be contributing to the obesity epidemic. Identifying the cause, and if it can be reversed, is an urgent priority.

## OTHER POTENTIAL ETIOLOGICAL FACTORS

### Urbanization

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

### Social Contagion

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

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

### Medication-Induced Weight Gain

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

### Dietary Sugar and Sugar-Sweetened Beverages

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

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

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

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

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

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

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

## SUMMARY

That the obesity epidemic lacks a clear explanation is a striking and poorly appreciated fact. The widely accepted causes of ever-increasing caloric intake and progressively declining

  

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

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

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

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

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

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

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

## THE REGULATION OF BODY WEIGHT

### ENERGY BALANCE

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

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

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

#### Energy Intake and Storage

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

Excess energy is stored as fat in adipose depots, carbohydrate (as glycogen) in liver, or protein in muscle. The energy density of adipose tissue is nearly 10-fold greater than liver (glycogen) or muscle (protein). The small storage capacity for carbohydrate can cover overnight energy needs during sleep. The larger

energy stores of fat are mobilized to cover longer-term energy shortages [70; 102; 103].

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

### Three States of Energy Balance

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

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

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

## DEFENSE OF BODY WEIGHT

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

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

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

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

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

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

## OVERVIEW OF CLINICAL MANAGEMENT

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

Knowledge of obesity pathophysiology, and clinical management based on the understanding of obesity as a chronic, progressive cardiometabolic disease, has rapidly evolved over the past decade. Consequently, some clinical practice guidelines on obesity from authoritative bodies have become outdated. For example, the most recent guideline by the AHA, American College of Cardiology, and The Obesity Society (AHA/ACC/TOS) was published in 2014 [118]. The paradigm of long-term management in this guideline is largely obsolete. A 2015 clinical practice guideline from the Endocrine Society and a 2016 guideline from the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) advanced the paradigm to the current standard of care, but available antiobesity medication options addressed in the guideline are non-recent [119; 120; 121]. Scientific statements by the Endocrine Society and clinical practice guidelines by the OMA, the American Gastroenterological Association (AGA), and the American Society for Metabolic and Bariatric Surgery (ASMBS) reflect current advances in obesity science, antiobesity medication options and their rational clinical use and bariatric surgical and noninvasive options [4; 7; 30; 122; 123; 124; 125; 126].

  

## THE FOUR PILLARS OF OBESITY MANAGEMENT

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

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

### Healthful Nutrition

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

### Physical Activity

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

### Behavior Modification

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


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

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

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

### Medical Management

#### *Antiobesity Medications*

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

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

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

| 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<br>Sulfonylureas<br>Insulin | DPP-4 inhibitors | Metformin<br>SGLT2 inhibitors<br>GLP-1R agonists |
| Antidepressants | Paroxetine<br>Amitriptyline<br>Mirtazapine | — | Bupropion<br>Fluoxetine |
| Atypical antipsychotics | Olanzapine<br>Quetiapine<br>Risperidone | Ziprasidone | — |
| Anticonvulsants and mood stabilizers | Divalproex<br>Carbamazepine<br>Gabapentin | Lithium<br>Lamotrigine | Zonisamide<br>Topiramate |
| Inflammatory rheumatic diseases | Corticosteroids | DMARDs<br>NSAIDs | — |
| DMARDs = disease-modifying antirheumatic drugs, DPP-4 = dipeptidyl peptidase-4,<br>NSAIDs = nonsteroidal anti-inflammatory drugs, SGLT2 = sodium-glucose cotransporter-2. | | | |
| *Source: [131]* | | | *Table 6* |

### *Bariatric Procedures*

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

## OBESOGENIC MEDICATIONS

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

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

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

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

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

## PRIORITIZATION FOR PATIENTS WITH OBESITY AND CARDIOMETABOLIC DISEASE

Patients with acute metabolic abnormalities (e.g., marked hyperglycemia, uncontrolled hypertension, severe hypertriglyceridemia, cardiovascular disease, cancer) should have these illnesses urgently assessed and treated, preferably with concomitant interventions that may also improve obesity [128]. For most patients without acute illness, treatment of obesity

  

is the priority, especially if the therapies chosen for treatment of the obesity are also expected to improve the complications of obesity [128]. In weight-loss pharmacotherapy, the initial priority should be to safely achieve maximal weight reduction, followed by sustained antiobesity medication and lifestyle therapy that may require less supervision to maintain the reduced body weight [132].

### TREATING TO TARGET WITH ANTIOBESITY MEDICATIONS

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

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

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

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

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

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

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

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

## ANTIOBESITY MEDICATIONS

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

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

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

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

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

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

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

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

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

## INDICATIONS FOR USE

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

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

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

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

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

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

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

**Strength of Recommendation**: Weak for

## FDA-APPROVED AGENTS

### For Monogenic Obesity Syndromes

#### *Setmelanotide (Imcivree)*

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

  

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

### *Bremelanotide*

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

### *Metreleptin*

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

## For Short-Term Use: Sympathomimetic Amines

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

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

### *Phentermine (Adipex-P, Lomaira)*

Phentermine HCl is a centrally acting sympathomimetic, with therapeutic effects mediated through increased levels of norepinephrine in the hypothalamus [123]. It was approved for short-term use in 1959 based on a 36-week trial that showed a mean placebo-subtracted weight loss of 8.2 kg [92]. Two more recent randomized controlled trials in Korea confirmed the short-term efficacy of phentermine, both showing significant weight reduction compared with placebo over 12 weeks [131]. Common adverse effects in clinical trials include dry mouth (55%) and insomnia (34%), without significant differences in systolic or diastolic blood pressure, headache, or palpitations between phentermine and placebo groups [131]. Other common side effects include dizziness, flushing, fatigue, and constipation [92]. Phentermine is not recommended for patients with cardiovascular disease, and uncontrolled hypertension is a relative contraindication. Phentermine is available in 8-mg tablets taken three times daily and in 15-mg, 30-mg, and 37.5-mg capsules taken once daily [131].

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

### *Diethylpropion (Tenuate)*

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

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

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

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

### *Other Medications*

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

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

## For Long-Term Use

### *Gelesis100 Oral Hydrogel (Plenity)*

Gelesis100 superabsorbent hydrogel is ingested orally, similar to drugs, but is regulated by the FDA as a class II medical device, because it acts mechanically as a transient, space-

occupying device in a swallowed capsule that absorbs water to expand and fill up the stomach to induce satiety. Gelesis100 is FDA approved for patients with BMI 25–40. Recommended dosing is three capsules (2.25 g/dose) with water before both lunch and dinner [30; 123].

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

### *Orlistat (Xenical, Alli)*

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

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

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

### *Phentermine/Topiramate ER (Qsymia)*

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

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

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

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

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

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

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

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

  

### *Naltrexone/Bupropion ER (Contrave)*

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

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

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

Common adverse effects of NB32 include nausea (30%), headache (14%), and constipation (15%), without significant differences in depression or suicidality events, insomnia, dizziness, or dry mouth between treatment and placebo groups [131]. NB32 has been shown effective in reducing HbA1c and is safe among subjects with type 2 diabetes taking oral antidiabetic agents [151]. NB32 can increase blood pressure and pulse despite weight loss [139]. While the cardiovascular safety of NB32 was investigated in the LIGHT trial, it was terminated prematurely after the study sponsor publicly released confidential favorable interim results after only 25% of expected vascular events had accrued, making it difficult to interpret the cardiovascular safety of this combination drug [131; 139].

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

GLP-1 RAs may be associated with increased risk of gallbladder or biliary diseases because GLP-1 inhibits gallbladder motility and delays gallbladder emptying by suppressing cholecystokinin secretion. The risk of gallbladder or biliary diseases was higher in trials for weight loss than diabetes control, which may relate to the greater weight loss, GLP-1 RA dose, or treatment duration [154]. When assessing potential risk to patients,

  

| 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* |

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 conclusions difficult. Gallbladder-related events have been reported to increase in persons with considerable weight reduction and are also observed with other obesity therapies, such as bariatric surgery and treatment with GLP-1 receptor agonists [133].

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

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

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

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

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

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

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

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

## INVESTIGATIONAL ANTIOBESITY MEDICATIONS IN CLINICAL TRIALS

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

### Cagrilintide

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

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

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

  

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

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

**Retatrutide (LY3437943)**

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

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

**Survodutide (BI 456906)**

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

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

**AMG-133**

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

**Bimagrumab (BYM338)**

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

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

**Orforglipron (LY3502970)**

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

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

**Danuglipron**

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

**Ecnoglutide**

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

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

**Mazdutide**

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

**APH-012**

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

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

**ARD-101**

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

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

**HU6**

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

**Nabilone**

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

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

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

**NNC9204-1177**

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

  

## CLINICAL USE OF ANTIOBESITY MEDICATIONS

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

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

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

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

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

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

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

### Practical Tips for Success with GLP-1 Agonists

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

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

### Demand and Supply Problems

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

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

| 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)<br>120 mg TID (Rx) | ~$45.00 (Alli)<br>$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* |

**Off-Label Prescribing of Antiobesity Medications**

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

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

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

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

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

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

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

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

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

  

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

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

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

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

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

## BARIATRIC SURGICAL PROCEDURES AND DEVICES

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

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

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

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

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

### 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.

| 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.<br>[a]Mean average. | | | |
| *Source: [127; 135; 202; 203]* | | | *Table 9* |

- Obesity-related complications: Replaces the term "weight-related complications," because patients with BMI <30 have not traditionally been considered MBS candidates.
- Pre-operative: The preferred term (rather than baseline) when referring to condition prior to MBS. May be notated with a p prefix (e.g., pBMI, pT2DM).

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

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

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

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

**PROPOSED MECHANISMS**

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

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

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

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

  

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

## INDICATIONS FOR BARIATRIC SURGERY

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

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

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

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

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

Level of Evidence: Expert Opinion/Consensus Statement

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

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

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

## PRE- AND POSTPROCEDURE RECOMMENDATIONS

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

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

### Preprocedure Evaluation and Medical Clearance for Bariatric Procedures

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

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

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

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

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

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

**Postoperative Nutritional Considerations**

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

**Procedure Selection**

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

**Other Issues**

***Preoperative Predictors of Outcome***

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

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

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

***Preoperative Denials or Delays of Approval for Insurance Coverage***

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

***Postoperative Esthetic Concerns***

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

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

**SURGICAL APPROACHES**

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

  

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

**Roux-en-Y Gastric Bypass (RYGB)**

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

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

*Efficacy*

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

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

**Sleeve Gastrectomy**

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

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

*Efficacy*

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

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

**Laparoscopic Adjustable Gastric Banding (LAGB)**

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

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

### *Efficacy*

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

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

### Biliopancreatic Diversion with Duodenal Switch (BPD/DS)

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

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

### *Efficacy*

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

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

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

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

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

### *Efficacy*

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

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

### One-Anastomosis Gastric Bypass (OAGB)

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

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

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

### *Efficacy*

OAGB showed substantial, durable weight loss in a trial involving 1,200 patients (pBMI: 46), with 6-, 9-, and 12-year BMI (28.5, 29.6, 29.9), excess BMI loss (83%, 78%, 76%), and excess weight loss (77%, 72%, 70%) all showing improvement. Approximately 70% of patients had data at 12 years [237]. Patients showed remission of presurgery type 2 diabetes (94%), insulin resistance (100%), hypertension (94%), hyperlipidemia (96%), GERD (92%), obstructive sleep apnea (90%), respiratory insufficiency (100%), and fatty liver (100%). In addition, improvement/remission was noted in osteoarthritis

  

(82%/18%) and urinary incontinence (78%/22%). All affected patients experienced improvement in polycystic ovarian disease. Complications included early severe events (2.7%), late severe events (1%), and bile reflux symptoms (2%). No followed patient required conversion for weight regain [237].

## ENDOSCOPIC BARIATRIC TECHNIQUES

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

### Endoscopic Sleeve Gastroplasty (ESG)

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

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

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

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

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

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

### Laparoscopic Gastric Plication

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

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

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

### Intragastric Balloon Devices

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

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

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

#### *Orbera Balloon Device*

Orbera, the most widely and longest used intragastric balloon device, is an endoscopically inserted single gastric balloon filled with 400–750 mL of fluid [245]. In a meta-analysis of 1,683 patients, weight loss at 6 and 12 months was 13.2% and 11.3%, respectively. Common adverse events were pain (34%), nausea (29%), GERD (18%), gastric mucosal erosion

(12%), and balloon removal due to intolerability (7.5%). Severe events included gastric ulcers (2.0%), balloon displacement (1.4%), small bowel obstruction (0.3%), perforation (0.1%), and death (0.08%). All perforations occurred in patients with prior gastric surgery; all deaths were secondary to perforation or aspiration. Thus, individualized, detailed risk assessment is necessary for patients planning to undergo intragastric balloon device placement [228]. Orbera early removal is also associated with use of selective serotonin or serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs) [125].

### *Obalon Balloon System*

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

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

### *ReShape Duo Balloon*

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

### *AspireAssist*

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

## OTHER OPTIONS

### The TransPyloric Shuttle (TPS)

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

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

### Vagal Nerve Blocking Therapy (Vbloc)

With vagal nerve blocking therapy, a pacemaker-like implantable device is surgically placed under the skin, with lead wires placed laparoscopically around the vagus nerve just above the stomach. Activation of the device causes intermittent vagal blockade to induce a sense of satiety. It is FDA approved for weight management in patients with BMI >40 or BMI >35 with weight-related complications [127; 135]. Contraindications include cirrhosis, portal hypertension, hiatal hernia, and other implanted devices (e.g., pacemakers, defibrillators) [127; 135].

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

### Liposuction

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

## IMPACT ON OBESITY-RELATED CARDIOMETABOLIC ENDPOINTS

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

  

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

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

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

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

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

## POSTBARIATRIC INTERVENTIONS

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

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

Surprisingly, nutritional, cognitive-behavioral, supportive, and other psychological and lifestyle interventions, started perioperatively or up to two years postoperatively, have not demonstrated a significant effect on overall weight loss. Systematic reviews and meta-analyses of these interventions have concluded their efficacy in preventing or reversing weight recurrence is marginal or null [224].

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

### Antiobesity Medication

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

Phentermine is one of the most commonly used antiobesity medications in MBS patients. Pairing phentermine with topiramate may be advantageous in weight-loss efficacy through combinatory mechanisms and cost considerations in post-MBS patients. GLP-1 agonists offer high efficacy, few drug interactions, and few side effects, but cost can be a deterrent [124].

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

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

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

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

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

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

**Revisions/Conversions**

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

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

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

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

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

## CONCLUSION

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

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

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

## APPENDIX: PHYSIOLOGY AND PATHOPHYSIOLOGY

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

### NEUROHORMONAL REGULATION OF ENERGY BALANCE AND BODY WEIGHT

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

  

provide homeostatic feedback of energy availability and status to the brain, they are called signals (of satiety, hunger, adiposity) [266].

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

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

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

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

**The Hypothalamus**

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

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

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

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

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

***The Arcuate Nucleus and the Melanocortin System***

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

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

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

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

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

### *Energy Balance and Melanocortin Activity*

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

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

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

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

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

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

### *Hypothalamic Regulation of Adiposity and Energy Expenditure*

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

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

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

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

### *Hypothalamic POMC Neurons and Cannabinoids*

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

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

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

### Brainstem Circuits

The gut communicates information about food ingestion to the brain via vagal afferent fibers in the NTS. Most of these signals act rapidly to promote meal termination, with less impact on energy expenditure or long-term food intake [150; 281]. The NTS receives and integrates the afferent vagal information and communicates this information to other brain regions it innervates [141; 282].

POMC neurons are also expressed in the NTS, where they project to and receive inputs from brain regions that both overlap and are distinct from connections of arcuate POMC neurons [269]. NTS POMC neurons respond to, among other things, gut-secreted CCK and adipocyte-derived leptin [271].

Some NTS neurons project to the parabrachial nucleus, a central node in this ascending pathway. An anorexigenic circuit implicated in satiety and meal termination arises from calcitonin gene-related peptide (CGRP) neurons in the parabrachial nucleus. Activation of CGRP neurons by gastric distention, CCK, and GLP-1 decreases appetite, while inhibition increases meal size [7; 266].

  

| 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<br>↓ Gastric emptying, food intake |
| Glucagon (GCG) | ARC, NTS | ↑ Satiety, glycogenolysis, gluconeogenesis |
| Insulin | ARC | ↓ Food intake, body weight |
| Pancreatic polypeptide (PP) | Hypothalamus, NTS | ↑ Satiety<br>↓ Gastric emptying |
| **Enteroendocrine cell origin** | | |
| Cholecystokinin (CCK) | Hypothalamus, NTS | ↑ Satiety<br>↓ Gastric emptying/motility |
| Ghrelin | ARC | ↑ Food consumption and reward |
| GIP | ARC, PVH, DMH | ↓ Food intake<br>↑ LPL, postprandial insulin |
| Glucagon-like peptide-1 (GLP-1) | ARC, NTS, AP, striatum | ↑ Satiety, postprandial insulin<br>↓ Gastric emptying/motility, food reward |
| Oxyntomodulin (OXM) | Hypothalamus | ↑ Satiety<br>↓ Gastric emptying, food intake |
| Peptide tyrosine tyrosine (PYY) | ARC, NTS | ↑ Satiety<br>↓ 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* |

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**

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

***Adipose Tissue and Pancreatic Hormones***

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

Leptin, the canonical signal of adipose tissue mass, is produced by white adipose tissue in approximate proportion to triglyceride stores. Adequate leptin action via its receptor (LepR) on arcuate neurons indicates sufficient energy stores; reduced leptin signaling indicates an energy deficit, promoting

hunger and increasing energy intake [281]. LepR activation also decreases body weight by increasing lipolysis and energy expenditure [277]. CCK potentiates leptin effects to decrease food intake and body weight [267].

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

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

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

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

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

### *Gut Peptide Hormones*

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

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

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

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

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

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

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

CCK is secreted postprandially and binds CCK1 receptors (CCK1R) expressed in the vagal afferents, brainstem, and hypothalamus to decrease food intake. The satiety signals of CCK are transmitted to the NTS by vagal sensory neurons.

  

CCK activates NTS POMC neurons, and brainstem MC4R signaling is required for CCK-induced appetite suppression [267]. CCK is an acutely acting signal with a very short half-life. Compensatory increases in meal frequency prevent CCK from producing long-term effects on total food intake or body weight [102].

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

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

## PATHOPHYSIOLOGY

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

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

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

### Adipose Cell and Tissue Function

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

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

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

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

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

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

#### *Lipid Storage*

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

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

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

### *Insulin Sensitivity*

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

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

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

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

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

### *Endocrine and Immune (Secretory) Function*

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

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

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

## Pathogenesis of Adiposopathy and Obesity-Related Complications

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

### *Local Pathogenesis*

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

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

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

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

  

### *Systemic Pathogenesis*

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

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

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

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

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

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

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

### *Biomechanical Consequences of Obesity*

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

### *"Metabolically Healthy" Obesity*

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

### *Psychiatric Disorders*

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

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

**Customer Information/Answer Sheet/Evaluation insert located between pages 56–57.**

## *COURSE TEST - #94280 PHARMACOLOGIC AND MEDICAL ADVANCES IN OBESITY MANAGEMENT*

*This is an open book test. Please record your responses on the Answer Sheet.*
*A passing grade of at least 70% must be achieved in order to receive credit for this course.*

*In accordance with the AMA PRA Category 1 Credit™ system,*
*physicians must complete and pass a post-test to receive credit.*

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

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

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

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

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

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

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

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

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

  

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

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

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

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

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

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

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

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

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

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

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

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

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

*Test questions continue on next page* →

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

*A) Patients older than 70 years of age should not be offered MBS.*
*B) MBS is recommended for patients with BMI of 40 only in those with at least one obesity-related complication.*
*C) A BMI >25 suggests clinical obesity in Asian patients, and those with BMI >27.5 should be offered MBS.*
*D) MBS should be considered in patients with BMI 25–30 who do not achieve substantial or durable weight loss.*

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

*A) Tobacco use, and cigarette smoking in particular, must be avoided at all times by all patients.*
*B) Patients who smoke cigarettes should stop as early as possible, preferably one year but at the very least six weeks before MBS.*
*C) Tobacco use should be avoided post-MBS given the increased risk of poor wound healing, anastomotic ulcer, and overall impaired health.*
*D) All of the above*

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

*A) Orbera*
*B) Obalon*
*C) ReShape Duo*
*D) TransPyloric Shuttle*

**25. Brown adipose tissue**

*A) comprises 15% to 25% of body fat.*
*B) has more mitochondria (thus its brown appearance).*
*C) includes subcutaneous adipose tissue and visceral (abdominal) adipose tissue.*
*D) is absent in neonates but increases in adults and increases further in obese adults.*

Be sure to transfer your answers to the Answer Sheet insert located between pages 56–57.
***PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.***

  

# Full Course Availability List

| ✓ | Course # | Course Title/Credits | Price |
|---|---|---|---|

## ALTERNATIVE MEDICINE

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| ☐ | 98010 | Cannabinoid Overview/3 | $26 |
| ☐ | 98020 | Commonly Abused Supplements/2 | $23 |
| ☐ | 98030 | Getting to the Point: Acupuncture and Acupoint Therapies/4 | $32 |
| ☐ | 98060 | Microbiome Medley: Pre-, Pro-, and Postbiotics/2.5 | $23 |
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| ☐ | 98090 | Understanding Glucosamine and Chondroitin/1.5 | $23 |
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| ☐ | 98394 | Herbal Medications: An Evidence-Based Review/10 | $68 |

## COMMUNITY HEALTH

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| ☐ | 91413 | Prescription Opioids: Risk Mgmt & Strategies for Safe Use/15 | $98 |
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| ☐ | 91764 | Bioterrorism: An Update for Healthcare Professionals/5 | $38 |
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## ETHICS - HUMAN RIGHTS

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| ☐ | 47174 | Medical Ethics for Physicians/5 | $38 |
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| ☐ | 97023 | Sexual Assault/3 | $26 |
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| ☐ | 97111 | Recognizing and Reporting Human Trafficking in Florida/2 | $23 |
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## GERIATRICS

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| ✓ | Course # | Course Title/Credits | Price |
|---|---|---|---|

## INFECTION CONTROL / INTERNAL MEDICINE

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| ☐ | 98533 | Smallpox Vaccination: An Update/5 | $38 |
| ☐ | 98593 | Multiple Sclerosis: A Comprehensive Review/10 | $68 |
| ☐ | 98623 | Foodborne Disease/10 | $68 |
| ☐ | 98643 | Infection Control: The New York Requirement/5 | $38 |
| ☐ | 98663 | Oral Pathology Review/5 | $38 |
| ☐ | 98703 | Chronic Pain Syn.: Current Concepts & Treatment Strategies/15 | $98 |
| ☐ | 98712 | Zika Virus Disease/3 | $26 |
| ☐ | 98721 | Bacterial Sexually Transmitted Infections/5 | $38 |
| ☐ | 98772 | Parkinson Disease/10 | $68 |
| ☐ | 98783 | Healthcare-Associated Infections/15 | $98 |
| ☐ | 98793 | Food Allergies/5 | $38 |
| ☐ | 98813 | Chronic Obstructive Pulmonary Disease (COPD)/10 | $68 |
| ☐ | 98883 | Sleep Disorders/10 | $68 |
| ☐ | 98903 | HIV/AIDS: Epidemic Update/5 | $38 |
| ☐ | 98932 | Irritable Bowel Syndrome/10 | $68 |

## MANAGEMENT

| | | | |
|---|---|---|---|
| ☐ | 41032 | Burnout in Physicians/5 | $38 |
| ☐ | 41170 | Professional Boundaries and Sexual Misconduct in Medicine/3 | $26 |
| ☐ | 41234 | OSHA and Healthcare Facilities/5 | $38 |
| ☐ | 41473 | Risk Management/5 | $38 |
| ☐ | 91012 | Family & Medical Leave: Law, Health Care, & Social Services/5 | $38 |
| ☐ | 91042 | Developing a Safe Opioid Treatment Plan for Managing Chronic Pain/1 | $23 |
| ☐ | 91053 | Health 2.0: Implications for Care/3 | $26 |
| ☐ | 91140 | HIPAA Privacy and Security/5 | $38 |
| ☐ | 91283 | Using Interpreters in Health and Mental Health Settings/5 | $38 |
| ☐ | 91334 | Medical Error Prevention and Root Cause Analysis/2 | $23 |
| ☐ | 91380 | Safe Handling of Hazardous Medications/2.5 | $23 |
| ☐ | 91404 | Clinical Trials: Considerations for Women and Ethnic Minorities/5 | $38 |

# Full Course Availability List *(Cont'd)*

| ✓ | Course # | Course Title/Credits | Price |
|---|---|---|---|

### MEDICAL / SURGICAL

| | | | |
|---|---|---|---|
| ☐ | 40943 | Acute Coronary Syndrome/15 | $98 |
| ☐ | 40953 | Moderate Sedation/5 | $38 |
| ☐ | 90072 | Migraine: Diagnosis and Therapeutic Advances/5 | $38 |
| ☐ | 90120 | Pulmonary Embolism/2 | $23 |
| ☐ | 90200 | Botulinum Toxin and Dermal Fillers for Facial Aging/10 | $68 |
| ☐ | 90214 | Diagnosing and Managing Headaches/10 | $68 |
| ☐ | 90240 | Pancreatic Cancer/10 | $68 |
| ☐ | 90284 | Ischemic Stroke/10 | $68 |
| ☐ | 90373 | Clinical Management of Ventricular Arrhythmias/15 | $98 |
| ☐ | 90424 | Seizures and Epilepsy Syndromes/10 | $68 |
| ☐ | 90444 | A Review of Interventional Radiology/10 | $68 |
| ☐ | 90471 | Safe Clinical Use of Fluoroscopy/10 | $68 |
| ☐ | 90563 | Disorders and Injuries of the Eye and Eyelid/15 | $98 |
| ☐ | 90683 | Oral Cancer and Complications of Cancer Therapies/5 | $38 |
| ☐ | 90744 | Transport Methods for Critically Ill Patients/15 | $98 |
| ☐ | 90773 | Skin Cancers/5 | $38 |
| ☐ | 90782 | Colorectal Cancer/15 | $98 |
| ☐ | 90804 | Antibradycardia Pacemakers/15 | $98 |
| ☐ | 90823 | Clinical Management of Atrial Fibrillation/10 | $68 |
| ☐ | 90844 | Hyperlipidemias & Atherosclerotic Cardiovascular Disease/10 | $68 |
| ☐ | 90983 | Bariatric Surgery for Weight Loss/5 | $38 |
| ☐ | 95001 | Expanding the Options: The Drug-Approval Process in the U.S./5 | $38 |

### MEN'S HEALTH

| | | | |
|---|---|---|---|
| ☐ | 93764 | Men's Health Issues/15 | $98 |
| ☐ | 93772 | Male Sexual Dysfunction/10 | $68 |
| ☐ | 93884 | Prostate Cancer/5 | $38 |

### PEDIATRICS

| | | | |
|---|---|---|---|
| ☐ | 92073 | Care of the Pediatric Trauma Patient/15 | $98 |
| ☐ | 92203 | Autism Spectrum Disorder/5 | $38 |
| ☐ | 92343 | Childhood Leukemias and Lymphomas/15 | $98 |
| ☐ | 92404 | Pediatric Abusive Head Trauma/1.5 | $23 |

### PHARMACOLOGY

| | | | |
|---|---|---|---|
| ☐ | 45121 | Strategies for Appropriate Opioid Prescribing: The Florida Req/5 | $38 |
| ☐ | 95073 | Antibiotics Review/5 | $38 |
| ☐ | 95082 | Antidepressant-Associated Sexual Dysfunction/1 | $23 |
| ☐ | 95102 | An Introduction to Pharmacogenetic Testing/1 | $23 |
| ☐ | 95131 | Prescription Opioids & Pain Mgmt: The Tennessee Guidelines/2 | $23 |
| ☐ | 95142 | Optimizing Opioid Safety and Efficacy/15 | $98 |
| ☐ | 95151 | Responsible and Effective Opioid Prescribing/3 | $26 |
| ☐ | 95172 | Medical Marijuana and Other Cannabinoids/5 | $38 |
| ☐ | 95211 | Responsible Prescribing of Controlled Substances: The LA Req/3 | $26 |
| ☐ | 95300 | Substance Use Disorders & Pain Mgmt: MATE Act Training/8 | $56 |
| ☐ | 95500 | Opioid Safety: Balancing Benefits and Risks/5 | $38 |

| ✓ | Course # | Course Title/Credits | Price |
|---|---|---|---|

### PSYCHIATRIC / MENTAL HEALTH

| | | | |
|---|---|---|---|
| ☐ | 96012 | Post-Traumatic Stress Disorder/15 | $98 |
| ☐ | 96102 | Frontotemporal Degeneration/2 | $23 |
| ☐ | 96154 | Alzheimer's Disease/15 | $98 |
| ☐ | 96182 | Anxiety Disorders/15 | $98 |
| ☐ | 96213 | Attention Deficit Hyperactivity Disorder/5 | $38 |
| ☐ | 96222 | Borderline Personality Disorder/15 | $98 |
| ☐ | 96313 | Human Trafficking and Exploitation/5 | $39 |
| ☐ | 96342 | Mental Health Issues Common to Veterans & Their Families/2 | $23 |
| ☐ | 96404 | Depression and Suicide/15 | $98 |
| ☐ | 96411 | Behavioral Addictions/15 | $98 |
| ☐ | 96423 | Cyberbullying and Harassment/5 | $38 |
| ☐ | 96431 | Mass Shooters and Murderers: Motives and Paths/15 | $98 |
| ☐ | 96442 | Suicide Assessment and Prevention/6 | $44 |
| ☐ | 96473 | Obsessive-Compulsive Disorder/4 | $32 |
| ☐ | 96563 | Alcohol and Alcohol Use Disorders/10 | $68 |
| ☐ | 96690 | Anxiety Disorders in Older Adults/3 | $26 |
| ☐ | 96790 | Psychedelic Medicine and Interventional Psychiatry/10 | $68 |
| ☐ | 96912 | Novel Psychoactive Substances: Trends in Drug Abuse/5 | $38 |
| ☐ | 96944 | Cocaine Use Disorder/5 | $38 |
| ☐ | 96954 | Methamphetamine Use Disorder/5 | $38 |
| ☐ | 96963 | Opioid Use Disorder/10 | $68 |
| ☐ | 96973 | Cannabis and Cannabis Use Disorders/5 | $38 |
| ☐ | 96983 | Hallucinogens/4 | $32 |
| ☐ | 96993 | Club Drugs/3 | $26 |

### WOMEN'S HEALTH - MATERNAL / CHILD

| | | | |
|---|---|---|---|
| ☐ | 93032 | Female Sexual Dysfunction/5 | $38 |
| ☐ | 93113 | Contraception/5 | $38 |
| ☐ | 93253 | Bleeding During Pregnancy/10 | $68 |
| ☐ | 93504 | Meanings of Menopause: Cultural Considerations/5 | $38 |
| ☐ | 93603 | Vaginal and Uterine Bleeding/5 | $38 |

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# Selected Course Availability List

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## MODERATE SEDATION

**#40953 • 5 Credits**

**Book By Mail – $38 • ONLINE – $30**

**Mandate: VA**

**Purpose**: The purpose of the course is to provide physicians with the information necessary to perform moderate sedation safely and according to existing guidelines in order to facilitate better patient care.

**Audience**: This course is designed for physicians in a variety of settings, including private practice, emergency department, radiology department, cardiac catheterization lab, and ambulatory surgery centers. The course is also of benefit to private practice physicians in family medicine and virtually all specialty areas.

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

**Special Approvals**: This course meets the Virginia requirement for 4 hours of anesthesia education.

## PROFESSIONAL BOUNDARIES AND SEXUAL MISCONDUCT IN MEDICINE

**#41170 • 3 Credits**

**Book By Mail – $26 • ONLINE – $18**

**Mandate: GA**

**Purpose**: The purpose of this course is to provide physicians and physician assistants with the knowledge and skills necessary to ethically and appropriately avoid boundary violations.

**Audience**: This course is designed for all physicians and physician assistants in all practice settings.

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

**Special Approvals**: This course meets the Georgia requirement for 2 hours of professional boundaries and sexual misconduct education.

## MEDICAL ETHICS FOR PHYSICIANS

**#47174 • 5 Credits**

**Book By Mail – $38 • ONLINE – $30**

**Mandate: CT, MA, MI, NV, PA, RI, TX**

**Purpose**: The purpose of this course is to briefly review the history, theory, and practical application of ethical principles to issues that arise in clinical practice. The goals of the course are to heighten awareness and promote self-reflection, address knowledge gaps, improve communication and decision-making skills, and promote reasonable, humane care for patients and families.

**Audience**: This course is designed for physicians and interested healthcare professionals.

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

**Special Approvals**: This course meets the Michigan, Nevada, and Texas requirements for ethics/professional responsibility education and meets the Connecticut, Massachusetts, Pennsylvania, and Rhode Island requirements for risk management education.

## PULMONARY EMBOLISM

NEW!

**#90120 • 2 Credits**

**Book By Mail – $23 • ONLINE – $15**

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

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

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

## ISCHEMIC STROKE

UPDATE

**#90284 • 10 Credits**

**Book By Mail – $68 • ONLINE – $60**

**Purpose**: The early identification and management of the risk factors for ischemic stroke can lead to substantial health benefits and reductions in cost. However, research has documented gaps between healthcare professionals' knowledge and practice with respect to prevention, demonstrating that adherence to evidence-based or guideline-endorsed recommendations pertaining to all interventions for primary and secondary prevention are underutilized or ineffective. The purpose of this course is to provide needed information about the roles of diagnosis and screening, timely evaluation of individuals with suspected stroke, immediate treatment of stroke, and the elements of effective rehabilitation programs so that healthcare professionals may implement the necessary interventions appropriately.

**Audience**: This course is designed for physicians, nurses, and physician assistants in the primary care setting. Neurologists and other healthcare practitioners will also benefit from this course.

**Additional Approvals**: ABIM, ABS, ABA

## SAFE CLINICAL USE OF FLUOROSCOPY

**#90471 • 10 Credits**

**By Mail – $68 • ONLINE – $60**

**Mandate: CA, MA (PAs)**

**Purpose**: The purpose of this course is to provide healthcare providers with an understanding of the challenges encountered when using fluoroscopy in clinical practice and the tenets of safe fluoroscopy use in clinical practice.

**Audience**: This course is designed for physicians, nurses, radiology technicians, surgical technicians, and all healthcare staff involved in ensuring safe clinical use of fluoroscopy.

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

**Special Approvals**: This course meets the California requirement for 4 hours of education in radiation safety for the clinical uses of fluoroscopy and 10 hours of education on the application of x-ray to the human body. This course meets the Massachusetts physician assistant requirement for 4 hours of fluoroscopic imaging education.

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# Selected Course Availability List *(Cont'd)*

## METABOLIC SYNDROME: A GROWING EPIDEMIC

UPDATE

**#91544 • 5 Credits**

**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.

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

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

## PRESCRIBING OPIOIDS, PROVIDING NALOXONE, AND PREVENTING DRUG DIVERSION: THE WEST VIRGINIA REQUIREMENT

**#91603 • 3 Credits**

**Book By Mail – $26 • ONLINE – $18**

**Mandate: WV**

**Purpose**: The purpose of this course is to provide clinicians who prescribe or distribute opioids with an appreciation for the complexities of opioid prescribing and the dual risks of litigation due to inadequate pain control and drug diversion or misuse in order to provide the best possible patient care and to prevent a growing social problem.

**Audience**: This course is designed for all physicians, physician assistants, and nurses in West Virginia who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.

**Additional Approvals**: ABIM, ABS, ABA

**Special Approvals:** This program has been approved by the WV Board of Medicine and will satisfy the required 3 hours of CME for Drug Diversion Training and Best Practice Prescribing of Controlled Substances Training for MDs and their licensed Physician Assistants.

## MATERNAL HEALTH DISPARITIES

NEW!

**#93010 • 4 Credits**

**Book By Mail – $32 • ONLINE – $24**

**Mandate: IL, NJ**

**Purpose**: The purpose of this course is to provide healthcare providers with the knowledge and skills necessary to improve maternal outcomes in all races, ethnicities, and marginalized groups.

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

**Additional Approvals**: ABIM, ABS, ABP

**Special Approvals**: This course meets the New Jersey requirement for 1 hour of implicit and explicit bias education for those who provide perinatal care and treatment to pregnant persons. This course meets the Illinois requirement for 1 hour of cultural competency education.

## PRESCRIPTION OPIOIDS AND PAIN MANAGEMENT: THE TENNESSEE GUIDELINES

**#95131 • 2 Credits**

**By Mail – $23 • ONLINE – $15**

**Mandate: TN**

**Purpose**: The purpose of this course is to provide clinicians who prescribe or distribute opioids with clinical guidance for management of chronic pain and opioid prescription drug use that conforms with Tennessee Department of Health guidelines and with clinical tools designed to assess the risk of drug-seeking and diverting behaviors. The goal is to promote best practice patient care and prevent the growing public health problem of drug misuse, diversion, and overdose.

**Audience**: This course is designed for all clinicians who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.

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

**Special Approvals:** This course is designed to meet the Tennessee requirement for 2 hours of education on the prescribing of controlled substances, including instruction in the Tennessee Chronic Pain Guidelines.

## ALZHEIMER DISEASE

Includes New Medications

**#96154 • 15 Credits**

**Book By Mail – $98 • ONLINE – $90**

**Mandate: CA, IL, MA**

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

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

**Additional Approvals**: ABIM, ABS, ABPath

**Special Approvals**: This course meets the Massachusetts requirement for cognitive impairment education and the Illinois requirement for 1 hour of Alzheimer's education. This course meets the California requirement for geriatrics education.

## SUICIDE ASSESSMENT AND PREVENTION

**#96442 • 6 Credits**

**By Mail – $44 • ONLINE – $36**

**Mandate: CT, NV, TX, WA**

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

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

**Additional Approvals**: ABIM, ABS, ABP

**Special Approvals**: This course meets the Connecticut requirement for 2 hours of behavioral health education. This course is approved by the Nevada State Board of Medical Examiners to fulfill 2 hours of Suicide Prevention and Awareness education. This course meets the Texas requirement for medical ethics/professional responsibility education. This course is approved by the State of Washington Department of Health to fulfill the requirement for Suicide Prevention training for healthcare professionals. Approval number TRNG.TG.60715375-SUIC.

# Selected Course Availability List *(Cont'd)*

## CANNABIS AND CANNABIS USE DISORDERS

**#96973 • 5 Credits**

**Book By Mail – $38 • ONLINE – $30**

**Mandate: NM, OR**

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

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

**Additional Approvals**: ABIM, ABS, ABP

**Special Approvals**: This course meets the New Mexico requirement for 2 hours of cannabis education and the Oregon requirement for 3 hours of medical marijuana education. This course meets 5 hours of addiction education.

## IMPLICIT BIAS IN HEALTH CARE

**#97000 • 3 Credits**

**Book By Mail – $26 • ONLINE – $18**

**Mandate: IL, MA**

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

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

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

**Special Approvals**: This course meets the Illinois and Massachusetts requirements for implicit bias training.

## SEXUAL ASSAULT

**#97023 • 3 Credits**

**By Mail – $26 • ONLINE – $18**

**Mandate: CT, SC, TX**

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

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

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

**Special Approvals**: This course meets the Connecticut requirement for sexual assault education, the South Carolina requirement for encouraged education in domestic violence, and the Texas requirement for forensic evidence education for those who perform examinations on sexual assault survivors.

## SEXUAL HARASSMENT PREVENTION: THE ILLINOIS REQUIREMENT

**#97081 • 1 Credit**

**By Mail – $23 • ONLINE – $15**

**Mandate: IL**

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

**Audience**: This course is designed for members of the interprofessional healthcare team who may act to prevent sexual harassment.

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

**Special Approvals**: This course is designed to fulfill the Illinois requirement for sexual harassment education.

## PALLIATIVE CARE AND PAIN MANAGEMENT AT THE END OF LIFE

**#97383 • 15 Credits**

**Book By Mail – $98 • ONLINE – $90**

**Mandate: CA, IA, MA, NJ, VT**

**Purpose**: The purpose of this course is to bridge the gap in knowledge of palliative care by providing an overview of the concept of palliative care and a discussion of the benefits and barriers to optimum palliative care at the end of life.

**Audience**: This course is designed for all members of the interdisciplinary team, including physicians, physician assistants, nurse practitioners, nurses, social workers, marriage and family therapists, and other members seeking to enhance their knowledge of palliative care.

**Additional Approvals**: ABIM, ABS, ABA

**Special Approvals:** This course fulfills 11 hours of education on the appropriate care of the terminally ill for California-licensed physicians who must complete 12 hours of pain management and the appropriate care of the terminally ill. This course meets the Iowa, Massachusetts, New Jersey, and Vermont requirements for end-of-life education.

## IMPLICIT BIAS: THE MICHIGAN REQUIREMENT


**#97440 • 2 Credits**

**ONLINE ONLY – $30**

**Mandate: MI**

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

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

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

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

## HUMAN TRAFFICKING AND EXPLOITATION: THE TEXAS REQUIREMENT

**#97471 • 5 Credits**

**By Mail – $38 • ONLINE – $30**

**Mandate: TX**

**Purpose**: 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.

**Audience**: This course is designed for Texas physicians, nurses, social workers, pharmacy professionals, therapists, mental health counselors, and other members of the interdisciplinary team who may intervene in suspected cases of human trafficking and/or exploitation.

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

**Special Approvals**: This course has been approved by the Texas Health and Human Services Commission (HHSC) to meet the requirement for human trafficking training.

# Selected Course Availability List *(Cont'd)*

## CHILD ABUSE IDENTIFICATION AND REPORTING: AN UPDATE FOR NEW YORK

**#97534 • 2 Credits**

**By Mail – $23 • ONLINE – $15**

**Mandate: NY**

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

**Audience**: This course is designed for all New York physicians, physician assistants, nurses, and other professionals required to complete child abuse education.

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

**Special Approvals**: This course is approved by the New York State Education Department to fulfill the requirement for 2 hours of training in the Identification and Reporting of Child Abuse and Maltreatment. Provider #80673.

## COMPLEMENTARY THERAPIES FOR MENOPAUSE

NEW!

**#98100 • 4 Credits**

**Book By Mail – $32 • ONLINE – $24**

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

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

**Additional Approvals**: ABIM, ABS

## INFECTION CONTROL: THE NEW YORK REQUIREMENT

**#98643 • 5 Credits**

**By Mail – $38 • ONLINE – $30**

**Mandate: NY**

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

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

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

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

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

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

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

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

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

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

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| ☐ | 95300 | Substance Use Disorders and Pain Management: MATE Act Training / 8 Credits | $48 |
| ☐ | 96790 | Psychedelic Medicine and Interventional Psychiatry / 10 Credits | $60 |
| ☐ | 94280 | Pharmacologic and Medical Advances in Obesity Management / 15 Credits | $90 |

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| ✓ | Course # | Course Title / Credits | Price |
|---|---|---|---|
| ☐ | 40953 | Moderate Sedation / 5 | $38 |
| ☐ | 41170 | Prof. Boundaries & Sexual Misconduct in Medicine / 3 | $26 |
| ☐ | 47174 | Medical Ethics for Physicians / 5 | $38 |
| ☐ | 90120 | Pulmonary Embolism / 2 | $23 |
| ☐ | 90284 | Ischemic Stroke / 10 | $68 |
| ☐ | 90471 | Safe Clinical Use of Fluoroscopy / 10 | $68 |
| ☐ | 91544 | Metabolic Syndrome: A Growing Epidemic / 5 | $38 |
| ☐ | 91603 | Prescribing Opioids: The WV Requirement / 3 | $26 |
| ☐ | 93010 | Maternal Health Disparities / 4 | $32 |
| ☐ | 95131 | Prescription Opioids & Pain Mgmt: TN Guidelines / 2 | $23 |
| ☐ | 96154 | Alzheimer Disease / 15 | $98 |
| ☐ | 96442 | Suicide Assessment and Prevention / 6 | $44 |
| ☐ | 96973 | Cannabis and Cannabis Use Disorders / 5 | $38 |
| ☐ | 97000 | Implicit Bias in Health Care / 3 | $26 |
| ☐ | 97023 | Sexual Assault / 3 | $26 |
| ☐ | 97081 | Sexual Harassment Prevention: The IL Req. / 1 | $23 |
| ☐ | 97383 | Palliative Care and Pain Mgmt at the End of Life / 15 | $98 |
| ☐ | 97440 | Implicit Bias: The MI Requirement (Online Only) / 2 | $38 Online Only |
| ☐ | 97471 | Human Trafficking and Exploitation: The TX Req. / 5 | $38 |
| ☐ | 97534 | Child Abuse Identification & Reporting: The NY Req. / 2 | $23 |
| ☐ | 98100 | Complementary Therapies for Menopause / 4 | $32 |
| ☐ | 98643 | Infection Control: The NY Requirement / 5 | $38 |

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Signature

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# Answer Sheet

(Completion of this form is mandatory)

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**Please note the following:**

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

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

Please refer to pages 27–28.

*Expiration Date: 04/30/26*

*May be taken individually for $48*

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

**#96790 PSYCHEDELIC MEDICINE AND INTERVENTIONAL PSYCHIATRY—10 CREDITS**

Please refer to pages 57–58.

*Expiration Date: 06/30/25*

*May be taken individually for $60*

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

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

Please refer to pages 104–106.

*Expiration Date: 11/30/26*

*May be taken individually for $90*

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

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# Evaluation

(Completion of this form is mandatory)

MD24

Last Name _____ First Name _____ MI _____

State _____ License # _____ Expiration Date _____

***To receive continuing education credit, completion of this Evaluation is mandatory.***

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

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

| #95300<br>8 Credits | #96790<br>10 Credits | #94280<br>15 Credits |
|---|---|---|
| 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. ☐ Yes ☐ No | 11. ☐ Yes ☐ No | 11. ☐ Yes ☐ No |
| 12. ☐ Yes ☐ No | 12. ☐ Yes ☐ No | 12. ☐ Yes ☐ No |
| 13. ☐ Yes ☐ No | 13. ☐ Yes ☐ No | 13. ☐ Yes ☐ No |

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

#96790 Psychedelic Medicine and Interventional Psychiatry — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

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

Signature _____

*Signature required to receive continuing education credit.*

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State License # Exp.

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Email

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## Please transfer your selected courses from pages 107–108 to this form.

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

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