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Management of Opioid Dependency During Pregnancy

Audience
This course is designed for pharmacists, substance abuse counselors, social workers, nurses, and any professional that assists women who are pregnant and misuse opioids. The material will also be useful for pediatric nurses working in the neonatal intensive care unit (NICU) and primary care providers in women's health care.

Course Objective
The purpose of this course is to provide healthcare professionals with the information necessary to appropriately care for pregnant women with opioid use disorder who are or are planning to become pregnant in order to minimize the adverse effects on the mother and fetus.

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

1. Identify the biologic effects of opioid use and misuse on women.
2. Describe the impact of opioid use on pregnancy and the importance of early recognition and prenatal care.
3. Outline preferred medications for opioid use disorder (MOUD) in patients who are pregnant.
4. Discuss the impact of opioid exposure in utero on fetal development and neonatal health.
5. Evaluate the important aspects of discharge planning for infants treated for neonatal abstinence syndrome.

Faculty
Davina Moss-King, PhD, CRC, CASAC, NCC, is the founder and President of Positive Direction and Associates, Inc., a consulting company that provides educational seminars for medical professionals in the community. Dr. Moss-King is a Certified Rehabilitation Counselor, a National Certified Counselor, and a Credentialed Alcohol and Substance Abuse Counselor and has been a substance abuse counselor for more than 25 years. She received her Master's Degree in Deafness Rehabilitation from New York University in 1998 and Doctorate degree with honors in Counselor Education from the State University of New York at Buffalo in 2005. Her dissertation was published as a book, Unresolved Grief and Loss Issues Related to Heroin Recovery, in 2009. In 2017, she published another book, The Positive Direction Model: Opioid Use and Pregnancy, which discusses a care model for pregnant women with opioid use disorder to ensure a successful pregnancy and delivery.

Dr. Moss-King's research interests include opioid use, the medical-patient relationship, and neonatal abstinence syndrome. She has written articles and continuing education courses and has also been a contributing author in three academic text books. Dr. Moss-King has been an adjunct professor at Canisius College's Counselor Education and Human Services Department since 2010 and is a member of the American Psychological Association and the National Association of Neonatal Therapists.

Faculty Disclosure
Contributing faculty, Davina Moss-King, PhD, CRC, CASAC, NCC, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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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

In recent decades, opioid use disorder (OUD) has become a global public health emergency, with trends in opioid prescribing for women in their reproductive years, in particular, continuing to be a major health concern [1; 2]. Estimates show that nearly 1 in 6 women of reproductive age (15 to 44 years of age) are prescribed opioids, and women are prescribed opioid medications for pain and for various medical ailments more often than men, causing complications such as insomnia, gastrointestinal side effects, tolerance, and dependence. The most common indication for opioid prescriptions for women is chronic pain management, but opioids may also be prescribed following surgery (e.g., cesarean section, hysterectomy) [2]. Oxycodone, hydrocodone, and codeine are among the most prescribed opioids, and each carries a risk for misuse [1]. The synthetic opioid pain reliever fentanyl is available by prescription but has gained traction in recent years as a common illicit street drug [18]. While opioids can be an effective analgesic, properties of these medications may cause patients to continue to seek the drug when the prescription runs out, thus contributing to misuse of opioids and the cycle of the opioid epidemic.

An extension of the opioid misuse epidemic is the public health issue of infants who are exposed to opioids in utero and who exhibit withdrawal symptoms at birth, known as neonatal opioid withdrawal syndrome (NOWS), or previously under the umbrella term of neonatal abstinence syndrome (NAS) [1; 2]. Local, national, and international reports from neonatal intensive care units (NICUs) have brought awareness to the issue of opioid use and misuse in women. The epidemic has affected cities and small towns alike and involves people of all races and ethnicities. As a result, more research has been conducted and programs have been established to heighten awareness of the relationship between opioid use, misuse, and dependence and maternal/fetal health. The U.S. Food and Drug Administration (FDA) require boxed warnings be available for all patients on all immediate- and extended-release opioid pain medications due to the potential for "addiction, abuse, and misuse, which can lead to overdose and death" [3]. In addition, the FDA requires labeling that if an opioid (immediate- or extended-release) is required for an extended period of time in a pregnant woman, the patient must be advised of risk of NOWS, which may be life-threatening if not recognized and treated. It is also advised that management by neonatology experts be available at delivery [3].

It is important to note that universal definitions regarding opioid abuse, misuse, and dependency are lacking; however, the text revised fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR), uses the term "opioid use disorder" to include misuse and abuse of or dependence on opioids. Previous editions of the DSM differentiated between the two categories. The DSM-5-TR combines abuse and dependence into a single disorder, measured on a continuum from mild to severe. In this course, opioid use disorder (OUD) and opioid dependence will be used interchangeably.

This course will highlight the biologic effects of OUD in women and fetuses. There will be an in-depth examination of the available pharmacologic treatments for the treatment of OUD during pregnancy, also known collectively as medications for opioid use disorder (MOUD) (previously medication-assisted treatment, or MAT), and the effects of treatment on the fetus. Lastly, there will be information regarding the long-term effects of in-utero exposure to opioids for the child.

BIOLOGIC EFFECTS OF OPIOIDS

According to the Centers for Disease Control and Prevention (CDC), women are prescribed opioids at higher doses and for longer periods of time than men [4]. While men continue to be more likely to die of prescription pain medication overdose, this gap is closing. In fact, since 1999, the percentage increase in deaths was more than 400% among women, compared with 265% in men [4].

Women between 25 and 54 years of age are most likely to be prescribed opioid pain medications, and 7 out of 10 prescription drug deaths among women involve opioids [4]. This may be due in part to the greater incidence of chronic pain syndromes in this patient population. Women who present with chronic pain are more likely than men to be diagnosed with two or more pain conditions and to be diagnosed with migraine headache, irritable bowel syndrome, fibromyalgia, arthritis, and low back, joint, or neck pain [5]. Studies have shown that men and women experience different side effects and responses to analgesic medications, which may be influenced by physiologic differences and/or social and psychologic factors. It has also been hypothesized that women may feel more pressure than men to maintain their familial roles as caretaker, spouse, mother, and/or provider despite pain, making their main objective when seeking medical intervention to cease pain and continue activities without interruption rather than seeking a curative, though more disruptive, option [6]. As a result, women may be prescribed opioid medications for a longer duration compared to men, and the duration and amount can lead to dependence. Female opioid abusers are also more likely to abuse other prescription medications, making drug-drug interactions a concern [5].

Opioids are defined broadly as all compounds related to opium—both natural products and synthetic derivatives. Opioids affect many body systems and share the following physiologic effects [5]:

- Analgesia
- Changes in mood and reward behavior
- Disruption of neuroendocrine function
- Alteration of respiration
- Changes in cardiovascular and gastrointestinal function

Potential side effects of opioid use include nausea, vomiting, constipation, dilation of the pupils, impaired ability to swallow, and an itchy feeling on the skin [7]. Women may suffer from secondary amenorrhea, defined as absence of menstruation for three or more months as a result of opioid use [7]. Because amenorrhea is relatively common, women may be unaware of their pregnancy and continue to use or abuse opioids, which can be harmful to the mother as well as the fetus. Other possible adverse effects of opioid use include sedation, cough suppression, dry mouth, and miosis.

WITHDRAWAL

Because many oral prescription opioids have half-lives of 24 to 36 hours, users often use at least daily to avoid withdrawal symptoms. Early symptoms and signs experienced during withdrawal include [5; 8]:

- Confusion
- Hallucinations
- Delirium
- Urticarial vasculitis
- Hypothermia
- Tachycardia

- Orthostatic hypotension
- Headache

Late symptoms of withdrawal include [5; 8]:

- Urinary retention
- Muscle rigidity
- Myoclonus
- Flushing
- Ureteric or biliary spasm

The most common symptoms are vomiting, diarrhea, profuse sweating, and tremor/shakiness [5; 8]. Withdrawal from opioids requires monitoring and medical management at a facility qualified to provide sensitive and intense care. The facility may be a hospital or an agency structured to specifically care for patients undergoing opioid detoxification. Medical management of detoxification and withdrawal in a specialty facility decreases the risk of injury or death from the withdrawal syndrome [9; 10]. With this approach, methadone or buprenorphine is given for approximately five days at slowly decreasing doses while the vital signs are monitored very closely. Although this method of detoxification is highly recommended for many patients, it is not recommended for pregnant women because of the harmful effects detoxification can have on the fetus [9; 10]. During pregnancy, dependent patients are often maintained on specific opioids and dosages in order to avoid withdrawal.

PREGNANCY IN PATIENTS USING OPIOIDS

Between 2010 and 2017, identification of OUD among pregnant women increased 131% at time of delivery. Recent estimates have shown that 7% of pregnant patients use prescription opioid pain relievers during pregnancy; of those, 1 in 5 reported misuse (defined as obtaining the drug without a prescription or using them for a reason not indicated) [1]. In addition, it has been shown that women who use opioids long-term before pregnancy tend to continue to use during pregnancy, and nearly 9 of 10 pregnancies among women with OUD are unintended [2]. Women who become pregnant while using opioids may be hesitant to obtain appropriate prenatal care for many reasons, including [1; 2; 11]:

- A history of amenorrhea may result in a delayed realization of pregnancy.
- The patient may lack access to health services and/or self-care practices.
- The patient may be in active addiction and be regularly participating in high-risk behaviors.
- The patient may not realize the importance of obtaining prenatal care.
- The patient may be fearful of stigma or legal considerations surrounding opioid use and pregnancy.
- The patient may be concerned about a treatment plan change that would allow pain to go unmanaged.

All patients taking opioids who can become pregnant should be advised of the warning signs of a possible pregnancy, including nausea while not in active withdrawal, tender breasts, sensitivity to unusual smells, and extreme fatigue, and should be instructed to seek immediate medical attention if any of these symptoms are observed [11]. For pregnant patients, actively using opioids is associated with an increased risk for obstetric and gynecologic complications such as pre-eclampsia, communicable infections (e.g., hepatitis C, human immunodeficiency virus [HIV]), low-birth-weight infants, stillbirths, pre-eclampsia, excessive bleeding, miscarriages, small head circumference in offspring, preterm deliveries, and even death [12; 13].

If pregnancy is suspected, a test should be administered. If positive, the immediate focus of care is on the health and safety of the mother and the fetus. The healthcare team may include community workers, a harm-reduction counselor, a chemical dependency counselor, and medical personnel (e.g., obstetrician/gynecologist, primary care physician, nurse practitioner) [14]. If a woman is under a physician's care for chronic pain and there is suspicion of pregnancy, the physician should assess the patient's medical condition prior to changing or refilling the patient's prescription. The potential risks of withdrawal and the short-and long-term effects on the fetus (e.g., developmental and congenital disabilities) should be included in patient education.

IMPACT ON FETAL DEVELOPMENT

Even in a supervised environment, opioid use during pregnancy can have negative effects on the fetus, and there is a significant risk of congenital birth defects. Infants born to mothers who used opioids during pregnancy may develop [29; 31]:

- Spina bifida
- Hydrocephaly
- Vision impairment, including glaucoma
- Hearing impairment
- Gastroschisis
- Cleft lip/palate
- Congenital heart defects (e.g., conoventricular septal defect, hypoplastic left heart syndrome, atrial septal defect, tetralogy of Fallot, pulmonary valve stenosis)

The heart and eyes appear to be most severely impacted, particularly in the first three weeks of pregnancy [11]. Long-term effects to offspring include language and cognitive deficits as well as behavior problems and issues with social acceptance by school-age peers [19].

Emerging research has found that infants born to mothers who used non-prescription fentanyl during pregnancy share a specific set of birth defects that include short stature, microcephaly, distinctive facial features, "rocker bottom" feet, broad thumbs, single palmar crease, and webbing of toes 2 and 3.

This syndrome seems to occur on a spectrum, and further research is required to substantiate the syndrome and identify the thresholds for abnormalities [18].

CONSIDERATIONS FOR WHOLE PERSON CARE OF THE PREGNANT PATIENT WITH OUD

In 2023, the Substance Abuse and Mental Health Services Administration (SAMHSA)published an advisory, *Evidence-Based, Whole-Person Care for Pregnant People Who Have Opioid Use Disorder*, which includes helpful points to consider when providing comprehensive patient-centered care and treating the whole person. The interdisciplinary team should consider the following points [10]:

- A safe living environment supports both a healthy pregnancy and recovery from OUD.
- Recovery is a highly personal process that occurs via many pathways.
- Counseling can help pregnant people engage and remain in OUD treatment by enhancing their coping skills and preventing recurrence.
- Peer workers, or nonclinical professionals with lived experience in behavior change and recovery from substance use disorder, can support pregnant people who have OUD during their recovery journeys.
- Pregnant people who have OUD need additional support in planning for labor and delivery.
- Pregnant people who have OUD need information about their options for pain relief during labor, delivery, and the postpartum period.
- Providers should assess and plan for the treatment of co-occurring mental disorders in pregnant patients who have OUD.
- Providers should help with planning for treatment of mental disorders if identified, recognizing that having a child can result in stress and sleep deprivation, which may make the condition worse or trigger a substance use recurrence.
- Providers should help connect pregnant people to the resources they need.
- Caring for pregnant people with OUD is empowering for the provider and patient.

MEDICATIONS FOR OPIOID USE DISORDER (MOUD) DURING PREGNANCY

In MOUD, methadone, buprenorphine, and buprenorphine/naloxone are used to avoid withdrawal symptoms in non-pregnant patients with OUD. Methadone and buprenorphine are rated pregnancy category C, meaning animal studies have shown an adverse effect on the fetus in the absence of human studies, but the potential benefits may warrant use in pregnant women despite the risks. Studies conducted through the SAMHSA have shown that naloxone can interfere with skeletal development and increase fetal mortality. Therefore, it is recommended that women taking buprenorphine/naloxone prior to becoming pregnant should be transferred to buprenorphine alone for the duration of the pregnancy. Overall, methadone and buprenorphine are the preferred medications used to stabilize the mother and fetus during pregnancy, and promising research has shown that neurological development in children of mothers who used MOUD is similar to those unexposed [9; 10; 29].

According to the World Health Organization, pregnant women dependent on opioids should be encouraged to use opioid maintenance treatment whenever available rather than to attempt opioid detoxification.

(https://www.who.int/publications/i/item/9789241548731. Last accessed December 14, 2023.)

Strength of Recommendation/Level of Evidence: Strong/Very Low

METHADONE

Methadone has been the criterion standard for opioid maintenance and avoidance of withdrawal during medically managed detoxification since the 1960s, and it remains the preferred option for the management of pregnant women dependent on opioids [9; 10]. As noted, methadone has been classified as pregnancy category C by the FDA because there is a lack of human studies. Although not approved by the FDA for OUD in pregnancy, patients who have been administered methadone properly, under medical supervision, have been found less likely to use other illicit drugs that could harm the fetus [15; 16].

Methadone maintenance therapy consists of an induction phase and a stabilization phase. The induction phase either continues the current methadone dose, if the patient was already using methadone pre-pregnancy, or starts an initial dose (based on weight, height, gestational age, and presence of withdrawal symptoms) if the patient has never taken methadone. If treatment is being initiated for the first time, it may be preferable for the patient to be admitted to an inpatient opioid treatment program for approximately 72 hours of observation. During the inpatient stay, the opioid levels and the physical status of the mother and the pregnancy are assessed [10; 19]. However, methadone induction is most often initiated in a licensed outpatient opioid treatment program, because inpatient care is not always available [17].

The average dose of methadone for pregnant women is 20–40 mg in the first trimester [9; 10]. As the fetus and placenta increase in size, a medical review is necessary to determine whether an increase of the dose of methadone is needed to avoid potentially harmful withdrawal symptoms. The dose is increased by 10 mg at each stage of significant growth; at the

end of the 36 weeks, the average dose is 70 mg. Immediately prior to delivery (38 to 40 weeks), the usual dose is 80 mg [9; 10]. After the birth, additional titration will be necessary, but the medication should be continued and not significantly reduced—the mother should be closely monitored during the postpartum period to avoid over-sedation [17]. An aftercare plan should also be in place for the safety of the mother and the child [19].

Methadone can be administered once per day in early pregnancy; however, as the pregnancy progresses, split dosing is recommended [10]. However, there has been a lack of empirical investigation of the effects on fetal and maternal plasma levels. As the dose increases, adverse effects are also more common, including sleep disturbances, excess weight gain, fluid retention, and intolerance to pain during delivery [10]. Any medications typically used for pain management during childbirth should be used with caution.

There are medical risks associated with methadone maintenance during pregnancy. One main concern is exposure of infants to the opioid in utero, resulting in withdrawal symptoms manifesting minutes to days later. Most symptoms develop within 72 hours after birth. As noted, this acute withdrawal from opioids is referred to as NOWS, and it is an expected and treatable outcome in infants born following methadone maintenance [1; 20]. Despite the risks, the benefits of methadone generally outweigh the negatives. Infants born to mothers on methadone maintenance are more likely to be born within the 36- to 38-week period and tend to be of average weight than children born to mothers with uncontrolled opioid use [9; 10].

BUPRENORPHINE

Another pharmacologic option for opioid maintenance during pregnancy is oral buprenorphine [17]. Clinical trials have determined that the efficacy of buprenorphine is comparable to methadone. This medication is prescribed for women who are unable to take methadone, or who were previously taking buprenorphine/naloxone, or who need an immediate change from another opioid [19].

Buprenorphine is usually self-administered on an outpatient basis, but it is also used in inpatient treatment programs. Various studies have found that administration of buprenorphine lowers the use of other drugs, increases the rate of treatment completion, and improves the likelihood of giving birth at term (between 38 and 40 weeks). Buprenorphine can be prescribed or dispensed in a medical office, greatly increasing access to treatment but also increasing potential for misuse. Thus, careful patient selection is critical, as this option has a higher potential for misuse than methadone [17; 19].

Unlike methadone doses, which can increase up to 80 mg, the dosage for buprenorphine is one 4–16 mg tablet per day in the induction period, with a maximum of 24–32 mg per day by the end of the pregnancy. The lower dosage results from the longer half-life (24 to 60 hours, compared to 24 to 36 hours for methadone) [10].

The birth outcomes with buprenorphine are the same as those outlined for methadone maintenance. However, compared with methadone exposure, infants exposed to buprenorphine in utero have less opioid in their system at birth as measured by urine, umbilical cord, and meconium drug testing and they display less severe NOWS symptoms [9; 10]. Patients on buprenorphine maintenance take one tablet per day for the duration of the pregnancy, making compliance easier than with the split doses of methadone. The FDA has also approved buprenorphine implants and buprenorphine injectables, but there is no safety data on its use during pregnancy [9; 10].

CONSIDERATIONS DURING DELIVERY FOR PATIENTS RECEIVING MOUD

All healthcare professionals caring for a woman during labor and delivery should be aware that she is undergoing MOUD [19]. As discussed, additional medications for pain relief may be necessary, as the maintenance dose of methadone or buprenorphine will not offer analgesia. The American College of Obstetricians and Gynecologists (ACOG) recommends offering epidural or spinal anesthesia for the management of pain in labor or delivery (when appropriate) and avoidance of narcotic agonist-antagonist drugs, such as butorphanol, nalbuphine, and pentazocine, as they may precipitate acute withdrawal [17].

NEWBORN ASSESSMENT FOR NEONATAL OPIOID WITHDRAWAL SYNDROME (NOWS)

Infants who have been exposed to opioids run a higher risk (30% to 80%) of developing NOWS, which can appear within 72 hours to 14 days after birth for methadone (resolving in several days to weeks) and within 12 to 48 hours after birth for buprenorphine (peak: 72 to 96 hours; resolving in seven days) [17; 20]. NOWS can also occur or be exacerbated in infants exposed or co-exposed to nicotine, benzodiazepines, and/or selective serotonin reuptake inhibitors in utero [17; 20; 21].

After delivery, the neonate should be assessed immediately for NOWS, the signs of which are generally apparent with routine newborn assessment and Apgar scores. Apgar scores are based on assessment of five categories (heart rate, respiratory effort, muscle tone, reflex irritability, and color) and are administered to all infants regardless of opioid exposure; however, special attention should be paid to possible signs of withdrawal in exposed infants [11]. The scores in each Apgar domain range from 0 to 2, with a maximum possible score of 10. The average score is 8 to 10, which indicates the infant does not need immediate attention. If the score is less than 8, the system affected is identified and appropriate medical procedures are initiated. If a third assessment at 10 minutes after birth does not show improvement, transfer to the NICU is warranted. Infants with acute NOWS usually have an Apgar score less than 8; however, there have been instances in which an infant's

Apgar score is within normal range at birth but then deteriorates and begins to show signs of NOWS within 3 to 12 hours [11]. Comparison studies have found no significant differences in Apgar scores at birth of infants exposed to buprenorphine compared to those exposed to methadone [22].

The signs of NOWS are a result of the effects of opioid withdrawal on the infant's neurologic, gastrointestinal, and autonomic systems [12]. Neurologically, the clinical signs of NOWS include irritability; staying awake for long periods of time/sleeping in short intervals; high-pitched crying and inconsolability; seizures; sneezing; stiff arms, legs, and back; and body tremors with or without a Moro reflex [13; 29]. NOWS may also compromise the infant's gastrointestinal system, resulting in vomiting, diarrhea, dehydration, and inadequate weight gain. High fever is common, and regulating the body temperature can be difficult. Elevations in respiration and blood pressure can occur [13]. Infants often appear uncomfortable and restless, even after being fed or swaddled.

If signs of NOWS are present, the infant should be taken to the NICU for further assessment and to determine the amount of opioid replacement (e.g., morphine) necessary to stabilize the patient, reverse the syndrome, and reduce the complications of withdrawal, if indicated. Additional medications (e.g., phenobarbital for seizures) may be required to control symptoms.

Several assessment tools are available and recommended to help determine the severity of NOWS (or NAS), including the Finnegan Neonatal Abstinence Scoring System, the Lipsitz Neonatal Drug-Withdrawal Scoring System, the Neonatal Withdrawal Inventory, the Neonatal Narcotic Withdrawal Index, and the Withdrawal Assessment Tool–Version 1 (WAT-1) [13; 17; 20; 26]. The Finnegan Neonatal Abstinence Scoring System is a 31-item scale that will quantify the severity of NAS/NOWS in order to help guide treatment decisions. The tool may be administered every four hours, and if an infant receives a score of 8 or more points, or the total for three consecutive scores is greater than 23, pharmacotherapy is indicated. In response to the complexity of the Finnegan tool, a shorter modified version is available (the Finnegan Neonatal Abstinence Syndrome Scale—Short Form) and is recommended by the American Academy of Pediatrics [24]. The Lipsitz Neonatal Drug-Withdrawal Scoring System consists of 11 items, and a score of 4 or greater is an indication that opioid therapy should be started. The Neonatal Withdrawal Inventory is an 8-point checklist of NAS/NOWS symptoms, with a 4-point behavioral distress scale. The Neonatal Narcotic Withdrawal Index is comprised of six items, for a possible maximum score of 12 points. A score of 5 or more on this index should prompt pharmacologic intervention [13]. Finally, the WAT-1 is administered to infants experiencing NAS/NOWS who have been exposed to opioids and benzodiazepines for an extended period (including throughout a pregnancy) [20]. With this tool, pharmacotherapy is recommended for patients who score 10 or more points. However, the relative efficacy of these scores has not been definitively proven [23].

Specific neonatal assessments for opioid withdrawal continue to be developed and are becoming more specific to NOWS sequelae. One such tool is the Maternal Opioid Treatment: Human Experimental Research (MOTHER) Neonatal Abstinence Measure (based on the Finnegan scoring system), which includes the addition of common central nervous system, gastrointestinal tract, and autonomic clinical signs. Another simplified tool to assist in quick assessment is the Eat, Sleep, Console (ESC) measure, which is guided by the infant's clinical signs of withdrawal through evaluation of an infant's ability to eat ≥1 oz or breastfeed well, sleep undisturbed ≥1 hour, and be consoled [13]. More research is required to prove the relative efficacy of these scales in screening for NOWS.

If indicated, opioid treatment should be initiated and the infant should be reassessed every three hours. Treatment with other sedatives (e.g., benzodiazepines, clonidine) has been effective, but 83% of physicians in the United States use an opioid (morphine or methadone) to treat NOWS [23]. The dose of replacement opioid varies according to the severity of symptoms and degree of exposure; the average initial dose of morphine sulfate is 0.05 mg/kg every three hours [5]. If there is no improvement after three hours, the dose may be increased to 0.08 mg/kg, then again to a maximum of 0.1 mg/kg every four hours if necessary. Stabilization may take up to 48 hours. After 24 to 48 hours of a constant morphine dose, a gradual weaning can begin. Even after morphine is discontinued, the infant should be monitored hourly for 48 hours. If signs of NOWS reappear, the original dose should be restarted and the same procedure followed until successful. After this, discharge plans may be implemented [13; 24].

DISCHARGE PLANNING FOR PATIENTS WITH OUD/NOWS

After NOWS has resolved and the infant is stabilized, the interdisciplinary team, together with the mother or caregiver, should work to create a discharge plan that will be conducive to the health and safety of the infant and the mother. It is important that infants continue to be physically supported and monitored for any signs of digression [13].

BREASTFEEDING

Breastfeeding is recommended for most infants, even if the mother is continuing MOUD, because it bonds the mother and infant, provides skin-to-skin contact, and confers immunity [17; 24]. Data from many systematic reviews support this recommendation. Some studies have shown that breastfeeding in these cases may also reduce the need for withdrawal treatment in infants [17; 24; 25]. According to the American Academy of Pediatrics, both methadone and buprenorphine are compatible with breastfeeding, regardless of maternal dose, as very minimal amounts are transferred to the infant. Having the infant remain in the same room as the mother is also preferable, as it facilitates breastfeeding and overall maternal involvement [17].

Overall, women who do not have health issues that could compromise the health of the infant or themselves should be encouraged to breastfeed their infants. Medical contraindications to breastfeeding include maternal HIV infection, active tuberculosis, continued use of illicit drugs, and some cancer treatments [19]. In the past, hepatitis C was considered a contraindication to breastfeeding, but this is no longer the case [10].

PATIENT EDUCATION AND REFERRALS

Most infants with NOWS are in the NICU for an average of 19 days (range: 7 to 32 days), and it is important to ensure that the child is discharged to a stable home. It should be noted that infants who remain in the same room as their mothers have shorter length of stays and are more likely to be discharged home [24; 27]. The discharge plan should include the infant's pediatrician, who will have access to the infant's record and a knowledge of any pharmacotherapy given and the length of stay in the hospital. Along with the pediatrician, the plan should include other members of the interdisciplinary team, including the mother's obstetrician/gynecologist, social workers, chemical dependency counselors, and supportive family members or friends [19]. Referral to additional specialty providers, as indicated, is critical at this point for both mother and baby to ensure minimal long-term negative health and cognitive consequences.

The mother and/or caregiver(s) should have a clear understanding of the aspects of caring for the child, especially if congenital abnormalities are present. The health and drug use of the mother or caregiver should also be properly assessed, either by an outpatient counselor or toxicology reports. Co-occurring mental health conditions, including depression and anxiety, are common in patients with OUD, and appropriate screening and treatment options should be explored. A social worker should determine if the home environment is safe for the child and the mother. Studies have shown that women with OUD report higher rates of intimate partner violence and are more likely to have poor pregnancy outcomes and adverse neonatal outcomes, including infants born with NOWS [28].

There is evidence that opioid exposure in utero can affect fine and gross motor coordination in offspring. In addition, cognitive delays have been noted throughout childhood, manifesting as short or poor attention span, hyperactivity, learning disability, and delayed speech and language development [29]. Studies have found that children with NOWS at birth were more likely to have developmental delays and lower IQ, were 2.3 times more likely to be admitted to the hospital for a neuropsychiatric disorder, and were more likely to show poorer performance on educational testing, meet criteria for a disability, require classroom therapies and services, and have lower attention compared with children who did not develop NOWS and unexposed controls [29]. It is important that follow-up continue with these children through their school years. Language delay assessments can be administered by a speech language pathologist when the child is approximately 2 years of age. If indicated by the results, early intervention plans may be created and involve the parent/caregiver, speech-language pathologist, occupational therapist, and pediatrician [29; 30].

CONCLUSION

Opioid use disorder has become a global public health emergency. Women (particularly in their reproductive years) are prescribed prescription opioids more often than men for a variety of conditions. While opioids can be an effective analgesic, properties of these medications may cause patients to continue to seek the drug when the prescription runs out, thus contributing to misuse of opioids and the cycle of the opioid epidemic. An extension of the opioid misuse epidemic is the public health issue of infants who are exposed to opioids in utero and who are at risk of experiencing symptoms of NOWS. Proper use of MOUD during pregnancy, thorough assessment at birth, and treatment of neonates with NOWS will ensure best outcomes for both parent and infant. Discharge planning includes education for caregiver(s), information on breastfeeding, and referrals for follow-up and specialty care, if indicated. As a member of the interdisciplinary healthcare team, compassionate management and treating the whole person will increase positive outcomes for this sensitive population and future generations.

COURSE TEST - #93093 MANAGEMENT OF OPIOID DEPENDENCY DURING PREGNANCY

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.

This 2 Hour activity must be completed by December 31, 2026.

1. Women are more likely than men to
- A) *be prescribed low-dose opioids.*
- B) *be diagnosed with osteoarthritis.*
- C) *be diagnosed with two or more pain conditions.*
- D) *die from a prescription pain medication overdose.*

2. Opioids share all of the following physiologic effects, EXCEPT:
- A) *Analgesia*
- B) *Enhanced cognition*
- C) *Alteration of respiration*
- D) *Changes in mood and reward behavior*

3. Which of the following is NOT a sign or symptom of opioid withdrawal?
- A) *Vomiting*
- B) *Myoclonus*
- C) *Bradycardia*
- D) *Tremor/shakiness*

4. Active use of opioids during pregnancy is associated with an increased risk for
- A) *pre-eclampsia.*
- B) *large-for-gestational-age infants.*
- C) *impaired pain sensation during delivery.*
- D) *All of the above*

5. The maximum daily dose of buprenorphine for MOUD during pregnancy is
- A) *4–16 mg.*
- B) *24–32 mg.*
- C) *40–60 mg.*
- D) *80–100 mg.*

6. Which of the following congenital defects is more common among infants exposed to opioids in utero?
- A) *Spina bifida*
- B) *Hydrocephaly*
- C) *Conoventricular septal defect*
- D) *All of the above*

7. Which of the following statements regarding the use of methadone as a medication for opioid use disorder (MOUD) during pregnancy is TRUE?
- A) *Methadone is considered pregnancy category D.*
- B) *Methadone should only be used in conjunction with naloxone.*
- C) *Methadone is the preferred option for opioid maintenance during pregnancy.*
- D) *Mothers who have been administered methadone properly are more likely to use other illicit drugs.*

8. Which of the following statements regarding neonatal opioid withdrawal syndrome (NOWS) is TRUE?
- A) *NOWS resolves within 24 hours of birth.*
- B) *NOWS only develops in infants exposed to opioids in utero.*
- C) *Infants with acute NOWS usually have a normal Apgar score.*
- D) *The signs of NOWS are the result of the effects of opioid withdrawal on the infant's neurologic, gastrointestinal, and autonomic systems.*

9. All of the following statements regarding the treatment of NOWS are true, EXCEPT:
- A) *After initiation of therapy, stabilization of infants with NOWS may take up to 48 hours.*
- B) *The majority of physicians in the United States use benzodiazepines to treat NOWS.*
- C) *The average initial dose of morphine for the treatment of NOWS is 0.05 mg/kg every three hours.*
- D) *Several assessment tools are available to help determine the severity of NOWS and the necessity for pharmacotherapy.*

10. Which of the following statements regarding breastfeeding and OUD is TRUE?
- A) *MOUD prevents mother-to-infant immunity normally provided by breastfeeding.*
- B) *Breastfeeding is not recommended until the mother can discontinue MOUD.*
- C) *Breastfeeding while taking MOUD may reduce need for withdrawal treatment in infants.*
- D) *All of the above*

Responsible and Effective Opioid Prescribing

This course meets the Louisiana requirement for controlled substances education for those pharmacists who hold a dangerous substance license.

Audience

This course is designed for pharmacy and other healthcare professionals who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.

Course Objective

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.

Learning Objectives

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

1. Apply epidemiologic trends in opioid use and misuse to current practice so at-risk patient populations can be more easily identified, assessed, and treated.
2. Create comprehensive treatment plans for patients with pain that address patient needs as well as drug diversion prevention.
3. Evaluate behaviors that may indicate drug seeking or diverting as well as approaches for patients suspected of misusing opioids.
4. Identify state and federal laws governing the proper prescription and monitoring of controlled substances.
5. Describe the available treatment modalities for opioid use disorder.

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

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Division Planner/Director Disclosure

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

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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

Pain is the leading reason for seeking medical care, and pain management is a large part of many healthcare professionals' practice. Opioid analgesics are approved by the U.S. Food and Drug Administration (FDA) for moderate and severe pain and are broadly accepted in acute pain, cancer pain, and end-of-life care, but are controversial in chronic noncancer pain. In response to the long-standing neglect of severe pain, indications for opioid analgesic prescribing were expanded in the 1990s, followed by inappropriate prescribing and increasing abuse, addiction, diversion, and overdose through the 2000s. In tandem with the continued under-treatment of pain, these practice patterns led to needless suffering from uncontrolled pain, opioid analgesic addiction, and overdose. Opioid analgesic prescribing and associated overdose peaked in 2011 with both now in multi-year decline.

Patients show substantial opioid response variations in analgesia and tolerability and may exhibit a range of psychologic, emotional, and behavioral responses that reflect inadequate pain control, an emerging opioid use problem, or both. Clinician delivery of best possible care to patients with pain requires appreciation of the complexities of opioid prescribing and the dual risks of inadequate pain control and inappropriate use, drug diversion, or overdose. A foundation for appropriate opioid prescribing is the understanding of factual data that clarify the prevalence, causality, and prevention of serious safety concerns with opioid prescribing.

SCOPE OF THE PROBLEM

Inappropriate opioid analgesic prescribing for pain is defined as the non-prescribing, inadequate prescribing, excessive prescribing, or continued prescribing despite evidence of ineffectiveness of opioids [1]. Appropriate opioid prescribing is essential to achieve pain control; to minimize patient risk of abuse, addiction, and fatal toxicity; and to minimize societal harms from diversion. The foundation of appropriate opioid prescribing is thorough patient assessment, treatment planning, and follow-up and monitoring. Essential for proper patient assessment and treatment planning is comprehension of the clinical concepts of opioid abuse and addiction, their behavioral manifestations in patients with pain, and how these potentially problematic behavioral responses to opioids both resemble and differ from physical dependence and pseudodependence. Prescriber knowledge deficit has been identified as a key obstacle to appropriate opioid prescribing and, along with gaps in policy, treatment, attitudes, and research, contributes to widespread inadequate treatment of pain [2].

The extent of opioid analgesic use in the United States in the 2000s was unprecedented in the country's history and unparalleled anywhere in the world. Before 1990, physicians in the United States were skeptical of prescribing opioids for chronic noncancer pain. In 2019, 22.1% of adults used a prescription opioid such as oxycodone and hydrocodone for chronic pain, and sales of opioid analgesics totaled approximately $7 billion in 2016 [3; 4].

Worldwide consumption of opioid analgesics has increased dramatically in the past few decades, with the United States driving a substantial proportion of this increase. For example, the 1990 global consumption of hydrocodone was 4 tons (3,628 kg), compared with the 2009 consumption of 39 tons (35,380 kg); 99% of this was consumed in the United States. Similarly, 3 tons (2,722 kg) of oxycodone were consumed globally in 1990, versus 77 tons (69,853 kg) in 2009, of which 62 tons (56,245 kg or 81%) were consumed in the United States [5]. With only 4.23% of the world's population, the United States annually consumes more than 80% of all opioid supplies, including [6; 7]:

- 99% of all hydrocodone
- 68% of all oxycodone
- 52% of all methadone
- 40% of all hydromorphone
- 19% of all fentanyl

This disproportionate rate of opioid consumption reflects sociocultural and economic factors and standards of clinical medicine.

Between 1992 and 2003, the U.S. population increased 14%, while persons abusing opioid analgesics increased 94% and first-time non-medical opioid analgesic users 12 to 17 years of age increased 542% [8]. It is interesting to note that while opioid prescribing has increased precipitously among adults in the United States, the rate remained low and steady for children between 1996 and 2012 [9]. A study using data from 2005 to 2015 showed opioid prescribing in 57 million visits from adolescents and young adults, representing a prescribing rate of nearly 15% in emergency departments and nearly 3% in outpatient clinical settings [10]. During the course of the study, emergency department prescribing decreased slightly while outpatient clinical setting prescribing remained the same [10]. To assist in monitoring the public health problem associated with prescribed opioids, numerous governmental, non-profit, and private sector agencies and organizations are involved in collecting, reporting, and analyzing data on the abuse, addiction, fatal overdose, and treatment admissions related to opioid analgesics.

Before it was halted in 2011, the Drug Abuse Warning Network (DAWN) provided estimates of the health consequences of nonmedical use of individual drugs, including opioid medications [11]. DAWN indicates that opioid abuse is a growing problem in the United States. In 2005 and 2011, hydrocodone and its combinations accounted for 51,225 and 97,183 emergency department visits, respectively. Oxycodone and its combinations resulted in 42,810 visits to the emergency department in 2005; this number increased to 175,229 visits in 2011 [12; 13]. Visits for nonmedical use of all opioids increased from 217,594 to 420,040 during the six-year period. In 2016–2017, there were 127,101 nonmedical opioid emergency department visits [14]. While this number is an improvement from previous years, nonmedical use accounts for 47.6% of all emergency department visits related to opioids [14].

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 [3; 15]. Initial treatment should always be considered individually determined and as a trial of therapy, not a definitive course of treatment [16].

In 2016, the CDC issued updated guidance on the prescription of opioids for chronic pain [3]. The guideline addresses when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use. In addition, the CDC further updated guidance against the misapplication of this guideline in 2019, noting that some policies and practices attributed to the guideline were inconsistent with the recommendations [17].

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 an updated guideline in 2022 [18]. 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 [18]. It is important to remember that inappropriately limiting necessary opioid medications to address patients' pain can be damaging and should be avoided. A central tenet of the updated 2022 guideline is that acute, subacute, and chronic pain needs to be appropriately and effectively treated regardless of whether opioids are part of a treatment regimen [18].

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 [3]. Payers and health systems should not use the 2022 guideline to set rigid standards related to dosage or duration of opioid therapy. The guideline is not a replacement for clinical judgment or individualized, patient-centered care [19].

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 [20; 21; 22].

CHRONIC PAIN

Nonpharmacologic therapy and non-opioid pharmacologic therapy are the preferred first-line therapies for chronic pain [18]. 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 [23]. 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 [18].

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 [1; 18]. The treatment plan should describe therapy selection, measures of progress, and other diagnostic evaluations, consultations, referrals, and therapies. Opioid therapy should not be initiated without consideration by the clinician and patient of an exit strategy to be used if opioid therapy is unsuccessful [18].

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 [1; 18]. When starting opioid therapy for chronic pain, clinicians should prescribe short-acting instead of extended-release/long-acting opioid formulations [18].

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 equivalent dose (MED) per day. Decisions to titrate dose to ≥90 mg MED/day should be avoided or carefully justified [17; 18].

The CDC recommends that clinicians should evaluate benefits and risks with patients within one to four weeks of starting opioid therapy for subacute or chronic pain or of dosage escalation. Clinicians should regularly re-evaluate benefits and risks of continued opioid therapy with patients.

(https://www.cdc.gov/mmwr/volumes/71/rr/rr7103a1.htm. Last accessed April 19, 2024.)

Strength of Recommendation/Level of Evidence: A4 (Most patients should receive based on clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations)

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 nonopioids and immediate-release opioids over long-acting/extended-release opioids. Taper opioid dose when no longer needed [18; 24].

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 [25]. 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 [25; 26; 27; 28].

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 [29]. This reluctance is related to a variety of attitudes and beliefs [25; 29]:

- 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 [30]. It is important to acknowledge patients' fears individually and provide information to help them differentiate fact from fiction [26]. For example, when discussing opioids with a patient who fears addiction, the clinician should explain that the risk of addiction is low [25]. 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 [25; 27; 29; 31]. 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 [29; 31]. As a result, many clinicians, especially primary care physicians, do not feel confident about their ability to manage pain in their patients [29; 31].

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 [26; 27]. Morphine, buprenorphine, oxycodone, hydromorphone, fentanyl, and methadone are the most widely used in the United States [32]. Unlike nonopioids, opioids do not have a ceiling effect, and the dose can be titrated until pain is relieved or side effects become unmanageable. For 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 [27]. Intramuscular injections should be avoided because injections are painful, drug absorption is unreliable, and the time to peak concentration is long [27].

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 1***) [33; 34].

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: [33; 34] *Table 1*

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 [18; 35].

Before deciding to prescribe an opioid analgesic, clinicians should perform and document a detailed patient assessment that includes [1]:

- 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 [1]. 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 [18; 24].

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 [33; 34].

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 [36].

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 [36; 37].

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 [36].

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 [38].

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 [36; 39]. Patients scoring lower on the DIRE tool are poor candidates for long-term opioid analgesia.

INFORMED CONSENT AND TREATMENT AGREEMENTS

The initial opioid prescription is preceded by a written informed consent or "treatment agreement" [1]. 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 [1]. 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" [1; 40]:

- 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 [41; 42]:

- 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 [1]. 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 [41; 42]:

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

Assessment Tools

VIGIL

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 [43].

Current Opioid Misuse Measure (COMM)

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 [35]. 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)?

Pain Assessment and Documentation Tool (PADT)

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 [44]. 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

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 [45].

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 2***) [46]. The CDC 2016 guideline 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 [3]. However, this recommendation was based on low-quality evidence that indicates little confidence in the effect estimate, and it is not included in the 2022 updated guideline [18].

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: [46] *Table 2*

Initially, testing involves the use of class-specific immunoassay drug panels [1]. 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 2021, nearly 14% 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 [47]. Benzodiazepines work by raising the level of the neurotransmitter gamma-aminobutyric acid (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 caution when prescribing benzodiazepines concurrently with opioids whenever possible [18]. 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. The rate of tapering should be individualized [18].

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 [1].

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 [1]. 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 [48].

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 [1]. 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 U.S. Food and Drug Administration (FDA) has developed a patient counseling guide 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 [49; 50].

When prescribing opioids, clinicians should provide patients with the following information [49]:

- 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 [51]. 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 [52]. 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 [52; 53]. 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 [53]. Patients should be advised to flush prescription drugs down the toilet only if the label or accompanying patient information specifically instructs doing so. In April 2023, the FDA issued a letter requiring all manufacturers of opioid analgesics dispensed in outpatient settings to submit a proposed modification to the Opioid Analgesic REMS. The modification requires manufacturers to make available prepaid mail-back envelopes to outpatient pharmacies and other opioid dispensers as an opioid analgesic disposal option for patients. The FDA expects to take action on this modification in 2024 [50].

The American College of Preventive Medicine has established best practices to avoid diversion of unused drugs and educate patients regarding drug disposal [51]:

- 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 [1; 18].

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 [48].

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 [54]. Among persons 12 years of age or older, 33.9% obtained their prescription opioids from a friend or relative for free, 39.3% got them through a prescription from one doctor (vs. 34.7% in 2019), 7.3% bought them from a friend or relative, and 3.7% took them from a friend or relative without asking [54]. Other sources included a drug dealer or other stranger (7.9%); multiple doctors (3.2%); and theft from a doctor's office, clinic, hospital, or pharmacy (0.7%) (vs. 0.9% in 2019) [54].

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 [55]. 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 [56].

In addition to aberrant urine screens, there are certain behaviors that are suggestive of an emerging opioid use disorder. The most suggestive behaviors are [48; 57; 58]:

- 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 [48; 57; 58]:

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

INTERVENTIONS FOR SUSPECTED OR KNOWN ADDICTION OR DRUG DIVERSION

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

Prevention is the best approach to addressing drug diversion. As noted, the most common source of nonmedical use of prescribed opioids is from a family member or friend, through sharing, buying, or stealing. To avoid drug sharing among patients, healthcare professionals should educate patients on the dangers of sharing opioids and stress that "doing prescription drugs" is the same as "using street drugs" [51]. 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 [51]. 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 [51].

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 [51]. 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 [59].

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 [60]. 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 [59].

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 [50]. 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 [41].

Several regulations and programs at the state level have been enacted in an effort to reduce prescription opioid abuse, diversion, and overdose, including [61]:

- 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 U.S. Drug Enforcement Administration (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 [62].

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 [63]. 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.

MANAGEMENT OF OPIOID USE DISORDER

Management of opioid dependence entails different methods to achieve different goals, depending on the health situation and treatment history of the patient. These treatment approaches include [64]:

- Crisis intervention: Directed at immediate survival by reversing the potentially lethal effects of overdose with an opioid antagonist.
- Harm reduction: Intended to reduce morbidity and mortality associated with use of dirty needles and overdose.
- Detoxification/withdrawal: Aims to remove the opioid of abuse from the patient's body, either through gradual taper and substitution of a long-acting opioid or through ultra-rapid opioid detoxification.

- Maintenance treatment or opioid (agonist) replacement therapy: Aimed at reduction/elimination of illicit opioid use and lifestyle stabilization. Maintenance follows detoxification/withdrawal, whereby the patient is tapered from short-acting opioids and introduced to a long-acting opioid agonist, such as methadone or buprenorphine. Patients remain on agonist therapy short-term, long-term, or indefinitely depending on individual needs.
- Abstinence-oriented therapy: Treatment directed at cure. The patient is tapered off of short-acting opioids during the detoxification/withdrawal process and may be placed on an opioid antagonist with the goal of minimizing relapse.

All treatment approaches share the common goal of improving health outcomes and reducing drug-related criminality and public nuisance [64].

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 [65]. The autoinjector delivers 0.4 mg naloxone intramuscularly or subcutaneously. The autoinjector comes with visual and voice instruction, including directs to seek emergency medical care after use [65]. 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 [66; 67; 68]. In 2023, the FDA approved Narcan, the first over-the-counter naloxone nasal spray [69]. Narcan is available as a 3-, 4-, or 8-mg single dose, administered in one nostril [70].

HARM REDUCTION

Harm reduction measures are primarily employed to minimize the morbidity and mortality from opioid abuse and to reduce public nuisance [38; 71]. 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 [38; 71].

DETOXIFICATION AND WITHDRAWAL

The process of tapering patients with opioid dependence from agonist therapy is often referred to as detoxification, or more accurately, medically supervised withdrawal [72; 73]. Its purpose is to eliminate physical dependence on opioid medications. It can be considered the medically supported transition to a medication-free state or to antagonist therapy. A careful and thorough review of the risks and benefits of detoxification should be provided, and informed consent obtained from patients prior to choosing this option [73; 74]. Detoxification alone should not be considered a treatment and should only be promoted in the context of a well-planned relapse-prevention program [64; 73]. Studies have shown that most patients with opioid use disorder who undergo medically supervised withdrawal will start using opioids again and will not continue in recommended care [75; 76; 77; 78; 79].

Discontinuation of opioid use must be implemented slowly and cautiously to avoid a marked abstinence syndrome. Withdrawal symptoms may not begin for days after abrupt discontinuation of methadone or buprenorphine given their longer half-lives. Protracted abstinence, or post-acute withdrawal, may last for several months and is characterized by asthenia, depression, and hypotension. Post-acute withdrawal is more likely to occur with methadone than other opioids [72].

The three primary treatment modalities used for detoxification are opioid agonists, non-opioid medications, and rapid and ultra-rapid opioid detoxification [72]. 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 [80]. Methadone is the most frequently used opioid agonist due to the convenience of its once-a-day dosing [72]. 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 [80]. Naltrexone is used following medically supervised withdrawal to help prevent relapse to opioid misuse [81].

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 [80; 82]. The first non-opioid treatment approved for the management of opioid withdrawal symptoms is lofexidine [83]. In studies, lofexidine resulted in less severe withdrawal symptoms and greater treatment retention than placebo.

However, some withdrawal symptoms, including anxiety and myalgias, are resistant to clonidine; benzodiazepines and nonsteroidal anti-inflammatory agents 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 [80].

Following detoxification, patients may feel exhausted and weak. Other complications, such as slight variations in hemodynamic status and gastrointestinal tract symptoms, follow quickly and may take several days to resolve. Muscle cramps and low back pain can be treated with nonsteroidal anti-inflammatory drugs. However, the newer cyclooxygenase-2 (COX-2) inhibitors may be advantageous because they produce fewer gastrointestinal side effects [80]. Insomnia is a frequent aspect of acute and protracted withdrawal, as opioids disrupt the normal sleep-wake cycle and many addicts require narcotics to sleep. Although long-term disruption of the normal sleep-wake cycle cannot be corrected rapidly, melatonin (3 mg), benzodiazepines, or antihistamines can be used with beneficial effects. Hypnosis and relaxation techniques are nonpharmacologic methods that may also be used [80]. Psychosocial treatments offered in addition to pharmacologic detoxification treatments positively impact treatment retention and completion, results at follow-up, and compliance [84; 85].

Ultra-Rapid Opioid Detoxification

Ultra-rapid opioid detoxification (UROD) has been developed as a means of avoiding the physical symptoms of withdrawal from opioids through the use of general anesthesia. UROD consists of naltrexone-assisted detoxification under heavy sedation or full anesthesia. UROD is also referred to as rapid or anesthesia-assisted detoxification. Other novel names for the process include [86]:

- UROD: General anesthesia; duration <6 hours
- Rapid opioid detoxification (ROD): Deep sedation; duration 6 to 72 hours
- Compressed opioid detoxification (COD) and naltrexone-compressed opioid detoxification (NCOD): Duration three to six days; preceded by a period of abstinence from opioids under sedation prior to introduction of naltrexone

The common underlying themes in all UROD techniques are a desire to condense the detoxification process into a shorter period to blunt the awareness of physical discomfort and to shorten the time lag between a patient's last dose of opioid and transfer to naltrexone maintenance [86]. This is accomplished by precipitating withdrawal following the administration of opioid antagonists under deep sedation or anesthesia.

Detoxification and withdrawal are rarely complete following UROD, and residual withdrawal symptoms can include drug craving, sympathetic hyperactivity, muscle pain, bone pain, nausea, vomiting, diarrhea, and insomnia. UROD does little to prevent protracted abstinence syndrome, which can last 3 to 10 weeks. Naltrexone may reduce opioid craving during the post-UROD period, with 50 mg per day recommended for relapse prevention. However, patients undergoing long-term naltrexone therapy can become sensitized to opioid drugs, heightening the risk of fatal overdose if opioid use is resumed [80].

A major shortcoming of UROD is the lack of evidence that an opioid antagonist can accelerate the restoration of neurobiologic homeostasis following opioid withdrawal [86]. Although significant drawbacks and questionable long-term efficacy exist with UROD, popular demand has proven difficult to restrain, in part due to the marketing of the procedure as a painless cure for opioid dependence. Marketing and the media have also blurred the fact that the original purpose of the procedure was to induce patients as rapidly as possible onto naltrexone and not to immediately permanently terminate years of opioid dependence [87].

Serious adverse events related to the anesthetic procedure also have been reported. A randomized, controlled trial directly comparing naltrexone-assisted detoxification with and without full anesthesia clearly stated that heavy sedation or full anesthesia should not be used because it does not confer any advantages in withdrawal symptom severity or increased rates of initiation or maintenance and it increases the potential for life-threatening adverse events [64]. A trial comparing naltrexone-induced, anesthesia-assisted detoxification with buprenorphine- or clonidine-assisted detoxification found no difference in withdrawal severity and rates of completion. However, potentially life-threatening adverse events associated with the UROD anesthesia were observed [88]. The risk for adverse events, the high monetary cost, and use of scarce intensive care resources suggest that this form of treatment should not be pursued [89; 90]. Additionally, UROD has not undergone the processes of therapeutic protocols, which are recognized as essential in scientific medicine, and no animal studies have been conducted with the procedure [87].

AGONIST REPLACEMENT OR ABSTINENCE THERAPY

Two principle treatment modalities are offered for patients with opioid dependence: agonist maintenance or detoxification followed by outpatient or residential drug-free treatment. Both can be effective, with no clear indication for each, although agonist maintenance leads to greater treatment retention [91]. A reasonable approach is initial outpatient or residential treatment referral for patients relatively new to treatment, with agonist maintenance appropriate for patients with history of treatment failures, greater disease severity, or a history of drug overdoses. Naltrexone is best reserved for patients with strong legal incentives to abstain, family involvement to monitor treatment, or concurrent enrollment and involvement in a psychosocial intervention [92].

At present, there are no direct interventions that are capable of reversing the effects of drugs of dependence on learning and motivation systems [93]. Instead, the management of opioid dependence often consists of pharmacotherapy with

methadone and buprenorphine, which do not eliminate physical dependence on opioids. These medications instead reduce the use of illicit opioids and produce very strong positive health outcomes as measured by decreased mortality, improved mental and physical health, and reduced risk of disease transmission [93]. Considering the high rate of relapse after detoxification, maintenance therapy with methadone or buprenorphine is currently considered to be the first-line treatment for patients with opioid dependence [64]. Both agents are superior to withdrawal management alone and both significantly reduce illicit opioid use [94].

Any treatment for opioid dependence 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 [64]. Patients who are dependent on opioids frequently suffer from physical and psychiatric disorders, and targeted interventions of psychiatric comorbidity are essential in improving treatment outcome for these patients [64]. Polysubstance abuse is the rule rather than the exception in opioid dependence, and concurrent use of other substances should be carefully monitored and treated when necessary [64]. Concurrent use of other drugs or active engagement in other addictive behaviors should lead to consideration of other treatment plan components for the patient. The presence of co-occurring substance use disorders should provoke a re-evaluation of the level of care in which the patient is treated [94]. 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 [64].

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 [72]. 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 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 [72].

The neurobiologic changes resulting from prolonged opioid exposure provide a rationale for specific pharmacotherapies, such as long-acting opioid agonists, that are aimed at stabilizing these complex systems [95]. Opioid agonist maintenance treatment stabilizes brain neurochemistry by replacing short-acting opioids, which can create rapid changes in opioid levels in the serum and brain, with a long-acting opioid that has relative steady-state pharmacokinetics. Opioid agonist maintenance treatment is designed to have minimal euphoric effect, block the euphoria associated with administration of exogenous opioids (competitive antagonism), eliminate the risk of infectious disease and health consequences associated with injection drug use, and prevent opioid withdrawal [95].

Successful maintenance treatment entails stabilization of opioid dependence through opioid receptor occupation. Positron emission tomography studies have revealed that only 25% to 35% of brain opioid receptors are occupied during steady-state methadone maintenance, suggesting that unoccupied opioid receptors disrupted during cycles of opioid abuse could normalize during methadone maintenance [72]. Additionally, opioid replacement therapy blocks much of the euphoria from illicit heroin use. Long-term opioid agonist treatment also has a positive impact on public health, through significantly reducing overdose deaths, criminal activity, and the spread of infectious disease [72].

As of 2020, there were 1,754 treatment programs including opioid replacement therapy in the United States [96]. However, this represents less than 20% of all patients with opioid use disorder. Although some have criticized the practice of methadone and buprenorphine therapy on the grounds that one opioid is merely being substituted for another, the clinical benefits strongly support this treatment modality [72]. When compared to active street heroin users, these benefits include a four-times lower HIV seroprevalence rates, 70% fewer crime-days per year, and a one-year mortality rate of 1% (versus 8%) [97].

Abstinence-Oriented Therapies

The primary goal of abstinence-oriented interventions is cure, which is defined as long-term, stable abstinence from all opioids. Abstinence is achieved in two phases: detoxification and relapse prevention. Outcomes in abstinence-oriented programs are generally poor [64].

The primary goal of pharmacotherapy during detoxification is to alleviate opioid withdrawal severity and associated distress/medical complications and to enhance patient motivation to continue treatment. Withdrawal can also be reduced by psychosocial measures, such as contingency management or counseling, and as discussed, the addition of psychosocial therapy to pharmacologic treatment increases efficacy. Buprenorphine and clonidine are both used to manage withdrawal symptoms, but buprenorphine's advantages, compared with clonidine, are related to its favorable side effect profile and positive effects on well-being and psychosocial variables [64].

12-Step/Self-Help Programs

Twelve-step programs for opioid abuse and dependence include Narcotics Anonymous (NA), Heroin Anonymous (HA), and Methadone Anonymous (MA) and are modeled after Alcoholics Anonymous (AA), an abstinence-based support and self-improvement program that is based on the 12-step model of recovery. AA has helped hundreds of thousands of

alcoholics achieve sobriety [98]. The 12-step model emphasizes acceptance of dependence as a chronic, progressive disease that can be arrested through abstinence but not cured. Additional elements include spiritual growth, personal responsibility, and helping other addicted persons. By inducing a shift in the consciousness of the addict, 12-step programs offer a holistic solution and are a resource for emotional support [98]. Although research on efficacy and patient outcomes in NA and MA is very limited, many prominent researchers emphasize the important role ongoing involvement in 12-step programs plays in recovery from substance abuse [99].

The understanding of drug dependence as a chronic and relapsing disorder has helped professionals gain a better comprehension of the vital role played by 12-step programs. Every patient attempting to recover from a substance use disorder will encounter a time when he or she faces urges to use without the resources or assistance of healthcare professionals. Twelve-step programs are not considered treatment, nor are they intended as substitutes for treatment. Instead, they are organizations that provide ongoing and indefinite support in the achievement and maintenance of abstinence and in personal growth and character development [99].

Part of the effectiveness of NA, HA, and MA is related to their ability to provide a competing and alternative reinforcer to drug use. Involvement in 12-step programs can enhance the quality of social support and the social network of the member, a potentially highly reinforcing aspect the person stands to forfeit if they resume drug using. Other reinforcing elements of 12-step involvement include recognition for increasingly durable periods of abstinence and frequent awareness of the consequences of drug and alcohol use through attendance of meetings [100]. Research shows that establishing a pattern of 12-step program attendance early in treatment predicts the level of ongoing involvement. Emphasis and facilitation of early engagement in a 12-step program involvement are key [101].

STIGMA OF ADDICTION

Many terms used in discussions of opioid use and misuse may have ambiguous meanings, and the absence of consensus in the terminology and definitions of substance use, substance use disorders, and addiction has led to considerable confusion and misconceptions. These misconceptions may be harbored by clinicians, patients, family members, and the public and can negatively impact patient interaction, assessment, treatment, and outcomes. This, coupled with pervasive stereotypes about what an opioid addict "looks" like, can negatively impact willingness to receive treatment or seek help and impair the patient's self-worth and mental health. Correction of these erroneous beliefs and attitudes is important, as is the use of nonpejorative and nonstigmatizing language when describing opioid analgesics, the patients who need them, and patients who develop aberrant behaviors or addiction involving opioids [31; 102]. It is important for all healthcare professionals to remember that addiction can affect any patients, regardless of age, sex, socioeconomic status, education, ability, or race.

PROGNOSIS OF TREATMENT FOR OPIOID USE DISORDER

The relapse rate among patients receiving treatment for opioid dependence and other substance abuse is high (25% to 97%), comparable to that of other patients with chronic relapsing conditions, including hypertension and asthma [103]. Many cases of relapse are attributable to treatment noncompliance and lack of lifestyle modification [104].

Duration of agonist replacement therapy is usually recommended as a minimum of one year, and some patients will receive agonist replacement therapy indefinitely. Longer durations of treatment are associated with higher rates of abstinence from illicit opioids [93].

Much remains unknown about patient outcomes following termination of long-term opioid replacement therapy. Some patients aim to achieve total abstinence from all opioids, but little is known about patient characteristics and strategies used among those who remain abstinent. It is likely that at least some of the patients who remain abstinent from all opioids do so with the help of a 12-step support program, such as NA [93].

CONCLUSION

Opioid analgesic medications can bring substantial relief to patients suffering from pain. However, the inappropriate use, abuse, and diversion of prescription drugs in America, particularly prescription opioids, has increased dramatically in recent years and has been identified as a national public health epidemic. A set of clinical tools, guidelines, and recommendations are now available for prescribers who treat patients with opioids. By implementing these tools, the clinician can effectively address issues related to the clinical management of opioid prescribing, opioid risk management, regulations surrounding the prescribing of opioids, and problematic opioid use by patients. In doing so, healthcare professionals are more likely to achieve a balance between the benefits and risks of opioid prescribing, optimize patient attainment of therapeutic goals, and avoid the risk to patient outcome, public health, and viability of their own practice imposed by deficits in knowledge.

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COURSE TEST - #95152 RESPONSIBLE AND EFFECTIVE OPIOID PRESCRIBING

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.

This 3 Hour activity must be completed by April 30, 2027.

1. Inappropriate opioid analgesic prescribing for pain is defined as
- A) *non-prescribing.*
- B) *inadequate prescribing.*
- C) *continued prescribing despite evidence of ineffectiveness of opioids.*
- D) *All of the above*

2. 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*

3. 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*

4. The Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)
- A) *consists of 5 items.*
- B) *is patient administered.*
- C) *diagnoses depression in the past month.*
- D) *assesses the likelihood of current substance abuse.*

5. Which of the following is NOT one of the 5 A's of monitoring chronic opioid response?
- A) *Analgesia*
- B) *Acceptance*
- C) *Affect (i.e., patient mood)*
- D) *Aberrant drug-related behaviors*

6. 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.*

7. 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*

8. 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.*

9. 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*

10. 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*

Child, Adolescent, and Adult Immunization Schedules

This course meets the Louisiana requirement for medication and vaccine administration education.

Audience

This course is designed for healthcare professionals working in all practice settings who may encourage patients to receive appropriate vaccinations and improve the overall vaccination rates.

Course Objective

There have been significant changes to the immunization schedules for children, adolescents, and adults, and the approval of multiple new vaccines has increased the opportunities for preventive care for both children and adults. However, coverage with some vaccines remains far below national goals, and outbreaks of vaccine-preventable diseases continue to occur. The purpose of this course is to provide healthcare professionals with the information necessary to identify patients who should be vaccinated and methods to increase vaccination coverage in outpatient practice.

Learning Objectives

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

1. Discuss the regulation of vaccines and identify the child, adolescent, and adult immunization schedules.
2. Explain the rationale behind the addition of new vaccines and changes to existing recommendations, and differences between current vaccines and newer options in development.
3. State contraindications to the administration of specific vaccines.
4. Explain recent safety data regarding vaccines.
5. Identify barriers to timely vaccination.
6. Describe methods for maximizing vaccination coverage.

Faculty

John J. Whyte, MD, MPH, is currently the Chief Medical Officer at WebMD. In this role, he leads efforts to develop and expand strategic partnerships that create meaningful change around important and timely public health issues. Previously, Dr. Whyte was the Director of Professional Affairs and Stakeholder Engagement at the FDA's Center for Drug Evaluation and Research and the Chief Medical Expert and Vice President, Health and Medical Education at Discovery Channel, part of the media conglomerate Discovery Communications. (A complete biography can be found at NetCE.com.)

Faculty Disclosure

Contributing faculty, John J. Whyte, MD, MPH, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner/Director Disclosure

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INTRODUCTION

Since the mid-1990s, a childhood vaccination schedule approved by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics, and the American Academy of Family Physicians has been published annually by the Centers for Disease Control and Prevention (CDC). A standardized adult immunization schedule has been published each year since 2002.

Over the years, there have been significant changes to the immunization schedules for children, adolescents, and adults. The approval of multiple new vaccines has increased the opportunities for preventive care for both children and adults. Yet, coverage with some vaccines remains far below national goals, and outbreaks of vaccine-preventable diseases continue to occur. The introduction of new vaccines, plus additional changes to the immunization schedules, makes it increasingly difficult for healthcare professionals to ensure that patients receive the recommended preventive care.

Changes in disease incidence illustrate the successes of widespread vaccination. Between 2000 and 2015, the incidence of acute hepatitis B declined in all age groups. Between 2015 and 2022, the rate has remained low and steady in most age groups. In 2022, the rate was highest (though still decreased from 2015) among persons 40 to 49 years of age and lowest among adolescents and children 19 years of age and younger [1]. Five years after the introduction of the heptavalent pneumococcal conjugate vaccine (PCV), the incidence of invasive pneumococcal disease (IPD) decreased by 82% among children 1 year of age and by 77% in children younger than 5 years of age [2]. The introduction of this vaccine in children appears to have reduced the incidence of IPD caused by covered strains in older adults as well [3].

However, for vaccines against communicable diseases to have the greatest impact, large proportions of the population must be covered. On a national scale, more than 90% of children have received age-appropriate doses of inactivated polio vaccine (IPV), measles/mumps/rubella (MMR), *Haemophilus influenzae* type b (Hib), hepatitis B (HepB), and varicella (VAR) vaccines by 24 months of age [4]. The Healthy People 2030 goal is to maintain a high level of coverage for these vaccines [114].

Certain vaccines remain significantly underutilized. For children birth to 24 months of age, completion of four doses of the heptavalent PCV (added to the immunization schedule in 2001) has been increasing but had reached only 82.3% in 2018, with no significant improvements since 2010 [4]. In 2018, full coverage with the hepatitis A vaccine (HepA) for all young children (by 35 months of age) was approximately 77.7%. Coverage with vaccines against rotavirus (by 8 months of age) was approximately 75.6% [4]. The influenza vaccination rate among children younger than 24 years of age remains low (60.6%), although this is higher than the overall rate for the U.S. population (49.2%). In 2018, 48% of adolescents were up to date on the human papillomavirus (HPV) vaccine [114]. This vaccine was considered too new to expect coverage to have met the national goal of 90% by 2020, particularly for teenage boys, for whom the recommendation was added in 2012. The Healthy People 2030 goal is for at least 80% coverage among all adolescents.

Undervaccination remains a concern among children even when national data show broad coverage. Coverage varies geographically and among different socioeconomic groups. Not all children receive their vaccinations on time, leaving them unnecessarily vulnerable [5]. Some parents opt out of vaccination entirely because of concerns about adverse effects or because they assume that the vaccine-preventable diseases are no longer a threat. There is also considerable misinformation about vaccine safety. However, recent measles outbreaks confirm that vaccination is still an important public health measure [4; 6].

In the adult population, vaccines are significantly underutilized (***Table 1***). For many years, the 23-valent pneumococcal polysaccharide vaccine (PPSV) has been recommended as a routine vaccination for adults 65 years of age and older, and

U.S. ADULT IMMUNIZATION RATES, 2018		
Vaccine	**Subgroup**	**Percent Vaccinated**
Influenza	50 to 64 years of age	46.9%
	65 years of age and older	68.8%
Pneumococcal disease	19 to 64 years of age, high risk	23.3%
	65 years of age and older	69.0%
Human papillomavirus	Women 19 to 26 years of age	52.8%
	Men 19 to 26 years of age	26.3%
Herpes zoster (shingles)	50–64 years of age	11.5%
	65 years of age and older	39.5%
Td or Tdap	19 years of age and older	62.9%
Hepatitis A	19 years of age and older	11.9%
Hepatitis B	19 years of age and older	30.0%
Td = diphtheria and tetanus toxoids, Tdap = diphtheria and tetanus toxoids and pertussis.		
Source: [7]		*Table 1*

multiple studies confirm that it can reduce the risk of IPD in this population. Yet according to estimates from the 2018 National Health Interview Survey, only 69.0% of adults in this age group have been vaccinated with PPSV [7]. Similarly, only about 47% of adults 50 to 64 years of age and about 69% of adults 65 years of age and older recalled receiving an influenza vaccination within the previous 12 months [7]. Even more than in the pediatric population, special effort may be needed to ensure that adults are aware of and have access to newer vaccines. In the first year after the herpes zoster vaccine was approved, only 2% of adults 60 years of age and older were vaccinated [8]. Attention to disparities is also needed. For example, Hispanics and non-Hispanic blacks are substantially less likely than whites to receive the influenza vaccine.

The following course will focus on the immunization schedules for children, adolescents, and adults, with an emphasis on vaccinations that are routine for most healthy persons. It will address the recommendations as of 2024, the rationale for the addition of new vaccines and for several potential new changes, contraindications and precautions as identified by the CDC and the ACIP, and methods to increase vaccination coverage in outpatient practice. The full schedules, including recommendations for patients with specific risk factors and catch-up schedules for patients who have missed doses, are available from the CDC.

Of note, the decision to vaccinate any individual patient should be based on a careful review of the patient's history and of current recommendations regarding each specific vaccine. The recommendation to vaccinate "all" children or adults with a given vaccine should not be interpreted to include those with contraindications or those for whom risks would outweigh benefits.

AN OVERVIEW OF IMMUNIZATION SCHEDULES

It is helpful to understand how vaccines are approved and then recommended as part of a schedule. The U.S. Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) is responsible for regulating vaccines in the United States. Vaccine clinical development follows the same general pathway as drugs and other biologics. A sponsor who wishes to begin clinical trials with a vaccine must submit an investigational new drug application (IND) to the FDA. The IND describes the vaccine, its method of manufacture, and the types of quality control testing done prior to administering the vaccine to humans. Also included is information about the vaccine's safety and ability to elicit an immune response in animal testing. In addition, the IND contains the proposed clinical protocol.

If the clinical trials are considered successful, a manufacturer will then submit a biologics license application. To be considered, the license application must provide the multidisciplinary FDA reviewer team with the efficacy and safety information necessary to make a risk/benefit assessment and to recommend or oppose the approval of a vaccine. In some cases, the FDA may present their findings to the Vaccines and Related Biological Products Advisory Committee. This non-FDA expert committee (consisting of scientists, physicians, biostatisticians, and a consumer representative) provides advice to the FDA regarding the safety and efficacy of the vaccine for the proposed indication. The FDA makes the final decision for/against approval but relies heavily upon the recommendation of its advisory committees.

It is also important to note that vaccine approval requires the provision of adequate product labeling to allow healthcare providers to understand the vaccine's proper use, including its potential benefits and risks. This information allows healthcare providers to communicate with patients and parents and to safely deliver the vaccine to the public.

FDA approval, however, does not guarantee that a vaccine will be considered routine. Rather, the CDC plays a critical role in determining the schedule. The ACIP consists of 15 experts in fields associated with immunization who have been selected by the Secretary of the U.S. Department of Health and Human Services to provide advice and guidance on the control of vaccine-preventable diseases. The Committee develops written recommendations for the routine administration of vaccines to children and adults in the civilian population; recommendations include age for vaccine administration, number of doses and dosing interval, and precautions and contraindications. The ACIP is the only entity in the federal government that makes such recommendations. These recommendations create the immunization schedules.

THE CHILD AND ADOLESCENT IMMUNIZATION SCHEDULE

In 1995, the first year that a harmonized childhood immunization schedule was published, there were only five items on the childhood immunization schedule, incorporating protection against nine diseases. Even then, a comment in the journal *Pediatrics* noted that the schedule's complexity could be confusing for both physician and patient [10]. The recommended shots were [11]:

- HepB
- Diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP), diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP), or tetanus and diphtheria toxoids vaccine (Td), depending on age
- Hib
- Oral polio vaccine (OPV)
- MMR

To achieve full coverage, children required a total of 15 shots and four oral doses spread out over at least six visits. DTaP has since replaced DTP and IPV replaced OPV without any changes in the necessary visits.

However, with the many new changes that have occurred, parents may be taken by surprise by the number of doses and visits their youngest children need. In 2013, the child and adolescent schedules were combined for the first time, resulting in one schedule for persons 0 to 18 years of age, a format that continues today (***Table 2***). This combined schedule contains vaccines against up to 16 infectious agents. Expansion of flu vaccine recommendations means annual visits. Other vaccines require multiple visits in the first year of life and at 11 or 12 years of age. Depending on the specific options used, full coverage can involve more than three dozen shots. A "catch-up" schedule for children and adolescents who fall behind on immunizations has also been established (***Table 3***).

Major changes to the annually published childhood schedule in the last decade have included [9; 11]:

- 2003: Influenza vaccination was to be "encouraged" for all children 6 to 23 months of age.
- 2004: Influenza vaccination was recommended for all children 6 to 23 months of age and close contacts of children 0 to 23 months of age.
- 2006: Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine replaced Td for adolescents, meningococcal conjugate vaccine (MCV) was recommended for certain age groups, and HepA was expanded to include all children, not just those in selected areas.
- 2007: Rotavirus and HPV vaccines were added. Influenza vaccination was expanded to all children 6 to 59 months of age. A second VAR dose was recommended for all children.
- 2008: The recommendation for MCV was expanded to include immunization of all children 11 years of age and older at the earliest opportunity.
- 2009: The recommendation for influenza vaccination was expanded to include children 6 months to 18 years of age (beginning with the 2008–2009 season).
- 2012: HPV vaccination recommendation extended to include boys 11 or 12 years of age.
- 2016: Meningococcal B vaccine added for high-risk children and adolescents 10 years of age and older.
- 2022: Dengue vaccine added for children and adolescents 9 to 16 years of age living in endemic areas who have had a laboratory-confirmed dengue infection.

Other changes to the childhood schedule have added to the potential for confusion. For example, there are two different rotavirus vaccines, with different numbers of doses. Understanding the differences is essential to these vaccines' safe and effective use.

Until 2009, a shortage of Hib had led to many children missing their 12 to 15 month booster dose; however, a new vaccine to cover that dose was approved during 2009 and has led to a recommendation that children 12 months to 4 years of age receive a catch-up dose at the earliest opportunity [13]. In mid-2009, the ACIP also made some changes and clarifications to the recommendations for IPV, including extending the minimum interval between doses 3 and 4 from four weeks to six months and noting that the final dose in the IPV series should be given when the patient is 4 years of age or older, regardless of the number of previous doses [14]. This updated recommendation also includes clarifications regarding the use of combination vaccines.

RECOMMENDED IMMUNIZATION SCHEDULE FOR PERSONS 0 THROUGH 18 YEARS OF AGE, 2024									
Vaccine	**Birth**	**1 mo.**	**2 mos.**	**4 mos.**	**6 mos.**	**9 mos.**	**12 mos.**	**15 mos.**	**18 mos.**
Respiratory syncytial virus (RSV-mAb [Nirsevimab])	1 dose depending on maternal RSV vaccination status[h]				RSV-mAb (1 dose)				
Hepatitis B	HepB	HepB			Hep B				
Rotavirus			RV	RV	RV[a]				
Diptheria, tetanus, acellular pertussis			DTap	DTap	DTap			DTap	
Haemophilius influenzae type b			Hib	Hib	Hib[b]		Hib[b]		
Pneumococcal conjugate (PCV15, PCV20)			PCV15, PCV20	PCV15, PCV20	PCV15, PCV20		PCV15, PCV20		
Inactivated poliovirus			IPV	IPV	IPV				
COVID-19					1 or more doses of updated (2023–2024) vaccine				
Influenza					IIV4 (yearly, 1 or 2 doses)				
Measles, mumps, rubella					MMR		MMR		
Varicella							VAR		
Hepatitis A					HepA[f]		HepA (2 doses)[c]		
Meningococcal ACWY			MenACWY-CRM (≥2 mos), MenACWY-TT (≥2 years)[d]						

RECOMMENDED IMMUNIZATION SCHEDULE FOR PERSONS 0 THROUGH 18 YEARS OF AGE, 2024								
Vaccine	**19–23 mos.**	**2–3 yrs.**	**4–6 yrs.**	**7–8 yrs.**	**9–10 yrs.**	**11–12 yrs.**	**13–15 yrs.**	**16–18 yrs.**
Diptheria, tetanus, pertussis			DTap			Tdap		
Haemophilius influenzae type b			Hib					
Pneumococcal conjugate			PCV15, PCV20					
Inactivated poliovirus			IPV					
Influenza	IIV4 (yearly, 1 or 2 doses)	IIV4 or LAIV (yearly, 1 or 2 doses)			IIV4 or LAIV (yearly, 1 dose)			
Measles, mumps, rubella			MMR					
Varicella			VAR					
Hepatitis A	HepA[c]	HepA						
Human papillomavirus					HPV[e]	HPV[e]		
Meningococcal ACWY	MenACWY-CRM, MenACWY-TT[d]					MenACWY		MenACWY
Meningococcal B						MenB-4C, MenB-FHbp		
Respiratory syncytial virus						Seasonal administration during pregnancy		
Dengue					DEN4CYD[g]			
Mpox								Mpox[i]

[a] If RV-1 is used, administer a 2-dose series at 2 and 4 months of age. If RV-5 is used, administer a 3-dose series at ages 2, 4, and 6 months.
[b] Administer a 3- or 4-dose Hib vaccine primary series and a booster dose to all infants. The primary series doses should be administered at 2, 4, and 6 months of age; however, if PRP-OMP is administered at 2 and 4 months of age, a dose at age 6 months is not indicated. One booster dose should be administered at age 12 through 15 months.
[c] Initiate the 2-dose HepA vaccine series for children aged 12 through 23 months; separate the 2 doses by 6 to 18 months.
[d] Minimum age: 2 months for Menveo (MenACWY-CRM) and 2 years for MenQuadfi (MenACWY-TT).
[e] Administer 2-dose series of HPV vaccine on a schedule of 0 and 6–12 months to all adolescents 11 to 12 years of age (minimum age: 9 years). A 3-dose series (0, 1–2, and 6 months) is recommended for persons who initiate at 15 years of age or later.
[f] For infants traveling to countries with high or intermediate endemic hepatitis A, 1 dose before departure; revaccinate with 2 doses, separated by at least 6 months, between 12 and 23 months of age.
[g] A 3-dose series (0, 6, and 12 months) only for those living in dengue-endemic areas AND with laboratory confirmation of previous dengue infection.
[h] For infants born in October through March whose mother did not receive RSV vaccine, who received the vaccine less than 14 days prior to delivery, or whose RSV vaccination status is unknown should receive 1 dose nirsevimab within one week of birth. For infants born between April and September whose mothers fit these criteria, 1 dose nirsevimab should be administered shortly before start of RSV season. All infants born to mothers who received RSV vaccine at least 14 days prior to delivery generally do not require vaccination.
[i] A 2-dose series administered 28 days apart recommended only for those 18 years of age and older who are at risk for Mpox infection.
□ = Range of recommended ages. ▭ = Certain high-risk groups only.

Source: [12] *Table 2*

CATCH-UP IMMUNIZATION SCHEDULE FOR PERSONS AGED 4 MONTHS THROUGH 18 YEARS WHO START LATE OR WHO ARE MORE THAN 1 MONTH BEHIND, 2024					
Vaccine	**Minimum Age for Dose 1**	**Minimum Interval Between Doses**			
		Dose 1 to 2	**Dose 2 to 3**	**Dose 3 to 4**	**Dose 4 to 5**
Children 4 months through 6 years of age					
Hepatitis B	Birth	4 weeks	8 weeks and at least 16 weeks after first dose. Minimum age for final dose: 24 weeks.	--	--
Rotavirus	6 weeks Maximum age for first dose: 14 weeks, 6 days	4 weeks	4 weeks Maximum age for final dose: 8 months, 0 days	--	--
Diphtheria, tetanus, pertussis	6 weeks	4 weeks	4 weeks	6 mos.	6 mos. (if necessary)
Haemophilius influenzae type b	6 weeks	4 weeks (if dose before 1st birthday). 8 weeks (as final dose) if first dose at 12 to 14 mos. If first dose at ≥15 mos., no further doses needed.	4 weeks (if current age <12 mos. and first dose administered at <7 mos. and at least one previous dose was PRP-T, DTaP-IPV-Hib-HepB, or unknown). 8 weeks and age 12 mos. through 59 mos. (as final dose) if current age is <12 mos. and first dose administered between 7 and 11 mos.; OR if current age is 12 through 59 mos. and first dose administered before 1st birthday and second dose administered at <15 months; OR if both doses were PRP-OMP and were administered before 1st birthday If previous dose at ≥15 mos., no further doses needed.	8 weeks (as final dose), only for children age 12 through 59 mos. who received 3 doses before 1st birthday.	--
Pneumococcal	6 weeks	4 weeks (if first dose before 1st birthday). 8 weeks (as final dose for healthy children) if first dose at ≥12 mos. No further doses needed for healthy children if first dose at ≥24 mos.	4 weeks (if current age <12 mos. and previous dose given at <7 mos.) 8 weeks (as final dose for healthy children) if current age ≥12 mos. and previous dose given at 7 to 11 mos. No further doses needed for healthy children if previous dose at ≥24 mos.	8 weeks (as final dose), only for children 12 through 59 mos. who received 3 doses before 12 mos. or for children at high risk who received 3 doses at any age.	--

Table 3 continues on next page

CATCH-UP IMMUNIZATION SCHEDULE FOR PERSONS AGED 4 MONTHS THROUGH 18 YEARS WHO START LATE OR WHO ARE MORE THAN 1 MONTH BEHIND, 2024 *(Continued)*

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to 2	Dose 2 to 3	Dose 3 to 4	Dose 4 to 5
Inactivated poliovirus	6 weeks	4 weeks	4 weeks if current age <4 yrs. 6 mos. (as final dose) if current age >4 yrs.	6 mos. (Minimum age for final dose: 4 years)	--
Meningococcal ACWY	2 months for MenACWY-CRM, 2 years for MenACWY-TT	8 weeks[a]	[a]	[a]	--
Measles, mumps, rubella	12 mos.	4 weeks	--	--	--
Varicella	12 mos.	3 mos.	--	--	--
Hepatitis A	12 mos.	6 mos.	--	--	--
Persons 7 through 18 years of age					
Tetanus, diphtheria; tetanus, diphtheria, acellular pertussis	7 years	4 weeks	4 weeks if first dose DTaP/DT before 1st birthday. 6 mos. (as final dose) if first dose of DTaP/DT or Tdap/Td at ≥12 mos.	6 mos. if first dose DTaP/DT before 1st birthday	--
Human papillomavirus	9 years	Routine dosing intervals are recommended.			
Hepatitis A	--	6 mos.	--	--	--
Hepatitis B	--	4 weeks	8 weeks and at least 16 weeks after first dose		
Inactivated poliovirus	--	4 weeks	6 mos. A fourth dose is not necessary if the third dose was administered at ≥4 years and at least 6 months after the previous dose.	A fourth dose indicated only if all previous doses administered <4 yrs. OR if third dose administered <6 mos. after second dose	--
Meningococcal ACWY	--	8 weeks	--	--	--
Measles, mumps, rubella	--	4 weeks	--	--	--
Varicella	--	3 mos. if age <13 years OR 4 weeks if age ≥13 years	--	--	--
Dengue	9 years	6 mos.	6 mos.		

[a] Administer MenACWY vaccine at age 13 through 18 years if not previously vaccinated. If the first dose is administered at age 13 through 15 years, a booster dose should be administered at age 16 through 18 years with a minimum interval of at least 8 weeks between doses. If the first dose is administered at age 16 years or older, a booster dose is not needed.

Source: [12] *Table 3*

RECOMMENDED ADULT IMMUNIZATION SCHEDULE BY VACCINE AND AGE GROUP, 2024					
Vaccine	**19–23 years**	**24–26 years**	**27–49 years**	**50–64 years**	**65 years and older**
COVID-19	1 or more doses of updated vaccine				
Influenza (IIV4, RIV4, or LAIV4)	1 dose (IIV4, RIV4, or LAIV4) annually[a]			1 dose (IIV4 or RIV4) annually[a]	
Respiratory syncytial virus	Seasonal RSV during pregnancy only				RSV[c]
Tetanus, diphtheria, pertussis (Td or Tdap)	One dose of Tdap, then boost with Tdap or Td every 10 years				
	One dose Tdap during each pregnancy; one dose Td for wound prophylaxis[a]				
Varicella	2 doses (if born in 1980 or later)[a]			2 doses[b]	
Human papillomavirus	2 or 3 doses[a]		2 or 3 doses[c]	–	–
Zoster (RZV)	2 doses (if immunocompromised)[b]			2 doses	
Measles, mumps, rubella	1 or 2 doses (if born 1957 or later)[a]				–
Pneumococcal 13-valent conjugate (PCV15, PCV20, PPSV23)	1 dose PCV20 OR 1 dose PCV15 followed by PPSV23[b]				1 dose PCV20 OR 1 dose PCV15 followed by PPSV23[a]
Hepatitis A	2,3, or 4 doses[b]				
Hepatitis B	2, 3, or 4 doses				2, 3 or 4 doses[b]
Meningococcal ACWY	1 or 2 doses, then booster[b] every 5 years				
Meningococcal B (MenB)	2 or 3 doses[c]	2 or 3 doses[b]			
Haemophilus influenzae type b (Hib)	1 or 3 doses[b]				
Mpox	2 doses[b]				

[a]For all patients in this category who lack evidence of immunity.
[b]Recommended if other risk factor is present.
[c]Recommended based on clinical decision-making.

Source: [19] *Table 4*

THE ADULT IMMUNIZATION SCHEDULE

As noted, the adult immunization schedule was created in 2002 to bring together the recommendations for routine vaccination of adults and to help healthcare professionals recall the specific needs of patients in certain chronic disease groups. The intention was to provide an up-to-date tool for providers to use in assessing patients' vaccination needs, creating standing orders and reminder systems, and otherwise reducing missed opportunities for vaccination [15].

The original adult schedule had a relatively short list of routine vaccinations for healthy persons, including [11]:

- Td every 10 years
- Annual influenza vaccine for adults 50 years of age and older
- PPSV for adults 65 years of age and older, with 1 booster for certain patients
- MMR (up to age 49 years) and varicella for those who are susceptible

Since that time, several changes have been made (***Table 4*** and ***Table 5***). The recommendation for routine vaccination against influenza was temporarily changed to age 65 years and older due to a vaccine shortage, but it has now returned to include all patients 6 months of age and older. Tdap is now recommended in lieu of one Td dose for adults up to 64 years of age. HPV vaccine is recommended for women and men up to 26 years of age, and the herpes zoster vaccine is routine for adults 60 years of age and older.

Since 2009, annual influenza vaccination has been recommended for all persons 6 months of age and older. The 2023–2024 influenza vaccine contained an H1N1-like antigen as well as H3N2 and two B antigens [20].

VACCINES AND RECOMMENDATIONS

Given the large number of vaccines now recommended, both parents and adult patients often have concerns about whether all the doses are needed. The following review of the rationale behind the changes to the child, adolescent, and adult immunization schedules is intended to help clinicians improve their own understanding and explain the rationale to patients.

VACCINES THAT MIGHT BE INDICATED FOR ADULTS BASED ON MEDICAL AND OTHER INDICATIONS, UNITED STATES, 2024					
Vaccine	**Pregnancy**	**Immuno-compromised (excluding HIV)**	**HIV infection**		**Men who have sex with men (MSM)**
			CD4+ <200 cells/mcL	**CD4+ ≥200 cells/mcL**	
COVID-19	1 or more doses of updated vaccine[a]				
Tetanus, diphtheria, pertussis (Td or Tdap)	1 dose Tdap each pregnancy	1 dose Tdap, then boost with Td every 10 years[a]			
Human papillomavirus (HPV)	Delay	2 or 3 doses through 26 years of age[a]			
Varicella	Contraindicated			2 doses[a]	
Zoster (RZV)	–	2 doses at 19 years of age		–	2 doses[a]
Measles, mumps, rubella	Contraindicated			1 or 2 doses[a]	
Influenza	1 dose annually[a] (LAIV contraindicated)				1 dose annually[a]
Respiratory syncytial virus (RSV)	Seasonal administration[a]	Seasonal administration[c]			
Pneumococcal (PCV15, PCV20, PPSV23)	–	1 dose PCV15 followed by PPSV23 or 1 dose PCV20[a]			Vaccinate if other risk factors[b]
Hepatitis A	2 or 3 doses[b]	–	2 or 3 doses[a]		
Hepatitis B	3 doses[b]		3 doses[a]		
Meningococcal ACWY	–		1 or 2 doses, then booster every 5 years[a]		–
Meningococcal B (MenB)	Exercise precaution	–			
Haemophilus influenzae type b (Hib)	–	3 doses post-stem cell transplant recipients only[a]	–		
Mpox	2 doses[b]				

VACCINES THAT MIGHT BE INDICATED FOR ADULTS BASED ON MEDICAL AND OTHER INDICATIONS, UNITED STATES, 2024 *(Continued)*					
Vaccine	**Heart disease, lung disease, chronic alcoholism**	**Asplenia, complement deficiencies**	**Chronic liver disease**	**Diabetes, end-stage renal disease, hemodialysis**	**Healthcare personnel**
COVID-19	1 or more doses of updated vaccine[a]				
Tetanus, diphtheria, pertussis (Td/Tdap)	1 dose Tdap, then boost with Td or Tdap every 10 years[a]				
Human papillomavirus (HPV)	2 or 3 doses through 26 years of age[a]				
Varicella	2 doses[a]				
Zoster (RZV)	2 doses ≥50 years[a]				
Measles, mumps, rubella	1 or 2 doses[a]				
Influenza	1 dose annually (exercise precaution with LAIV)[a]	1 dose annually (LAIV contraindicated)[a]	1 dose annually (exercise precaution with LAIV)[a]		1 dose annually[a]
Respiratory syncytial virus (RSV)	Seasonal administration[c]				
Pneumococcal polysaccharide (PCV15, PCV20, PPSV23)	1 dose PCV15 followed by PPSV23 or 1 dose PCV20[a]				1 dose PCV15 followed by PPSV23 or 1 dose PCV20[b]
Hepatitis A	2 or 3 doses[b]		2 or 3 doses[a]	2 or 3 doses[b]	
Hepatitis B	2, 3, or 4 doses depending on vaccine or condition[a]				
Meningococcal ACWY	–	1 or 2 doses, then booster every 5 years[a]	–		
Meningococcal B (MenB)	–	2 or 3 doses[a]	–		
Haemophilus influenzae type b (Hib)	–	1 dose for asplenia only	–		
Mpox	2 doses[b]				

[a] For all patients in this category who lack evidence of immunity.
[b] Recommended if other risk factor is present.
[c] Recommended based on shared clinical decision-making.

Source: [19] *Table 5*

SEASONAL INFLUENZA

Recommendation for Children: Influenza vaccine is recommended annually for children 6 months through 18 years of age. Two doses, separated by at least four weeks, should be given to children if they are receiving influenza vaccine for the first time. Also give two doses if the child was vaccinated for the first time the prior season but received only one dose. For the 2023–2024 season, use of live attenuated influenza vaccine (LAIV) may be considered for children 2 years of age and older.

Recommendation for Adults: Vaccination is recommended annually for all adults without a contraindication with inactivated influenza vaccine (IIV), recombinant influenza vaccine (RIV), or live attenuated influenza vaccine (LAIV). Other options include high-dose or adjuvanted IIV for adults 65 years of age or older. Women who are or may become pregnant should not receive LAIV.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Advisory Committee on Immunization Practices (ACIP), routine annual influenza vaccination is recommended for all children 6 months through 18 years of age.

(https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf. Last accessed May 24, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

The expansion of the recommended ages for the vaccination of children and adults against influenza is one of the most significant changes to the schedule in recent years. It requires an annual visit to a healthcare provider, including among older children and young adults who typically have low rates of physician visits.

The ACIP considered multiple factors in making this recommendation. First, according to accumulated evidence, the influenza vaccine appears to be both safe and effective, with the benefits of vaccination outweighing the small risk of adverse effects [21]. Widespread vaccination is also intended to lower the social and economic impact of influenza. The number of missed days of school for children and missed days of work for parents is substantial. Physician visits for the flu may lead to a prescription for antibiotics—treatment that is unnecessary and potentially dangerous.

The recommendation is also intended to simplify the decision to advise vaccination for children [21]. In previous years, vaccination was recommended for a number of groups with specific risk factors. These included older children with certain medical conditions and children who were close contacts of people who should be immunized. Making vaccination routine for all children is expected to lead to a 50% increase in coverage for those children who have a specific risk-based or contact-based indication.

Another change, for both children and adults, was the development of LAIV, a nasal-spray vaccine that can be easier for some patients to accept than an injection [22]. Data from the 2015–2016 flu season found an only 3% efficacy rate with LAIV (compared with 63% with IIV), and LAIV was not recommended between the 2015 and 2018 seasons [19; 20]. However, the 2018–2019 influenza guideline reintroduced LAIV as an option for persons 2 to 49 years of age for whom it is appropriate, and it remains an option in the 2023–2024 guideline [20]. This excludes women who are pregnant and those with HIV, immunocompromise, asplenia, and/or complement deficiencies.

In the past, egg allergy (beyond urticaria) was considered a contraindication or cause for additional safety measures when influenza vaccination was considered. However, it is now recommended that all persons 6 months of age or older with egg allergy should receive any influenza vaccine (egg-based or non-egg-based) that is otherwise appropriate for the recipient's age and health status [20]. It is no longer recommended that persons who have had an allergic reaction to egg involving symptoms other than urticaria should be vaccinated in an inpatient or outpatient medical setting supervised by a healthcare provider who is able to recognize and manage severe allergic reactions if an egg-based vaccine is used.

TETANUS/DIPHTHERIA/PERTUSSIS

Recommendation for Children: DTaP is recommended at 2, 4, 6, and 15 to 18 months of age (or as early as 12 months, if 6 months have passed since the last dose) and at 4 to 6 years of age. Tdap is recommended at 11 to 12 years for children who have completed the recommended childhood DTP/DTaP vaccination series and have not received a Td booster dose and for older children who have not received a dose. If a child has already received Td, a five-year interval before Tdap is encouraged unless pertussis protection is specifically needed.

Recommendation for Adults: Td or Tdap booster every 10 years. Tdap replaces one Td dose for adults who have not already received Tdap. (See immunization schedule for special situations, including adults who have not received primary childhood vaccination and pregnant women.)

The inclusion of Tdap on the adult immunization schedules may create confusion because it replaces a dose of Td that was previously routine and patients may be uncertain about which vaccine they received. However, Tdap also has the potential to make an important impact on the public's health [23]. In the past, vaccination against pertussis was given only during young childhood. However, immunity against pertussis declines within about 5 to 10 years [23; 116]. Reported cases of pertussis increased steadily from the 1980s to a peak in 2014. In 2021, 2,116 cases were reported—a decrease of more than 88% since 2019—but many more go undiagnosed and unreported [24]. Infants younger than 1 year of age are at highest risk and continue to have the highest reported rate of pertussis; nearly half require hospitalization. Adolescents 11 to 19 years of age and adults 20 years of age and older accounted for approximately 66.2% of reported cases in 2021; cases among

children 7 to 10 years of age accounted for approximately 3.5% of reported cases [24]. Adults may also have complications including pneumonia, rib fracture, and loss of consciousness ("cough syncope") [25]. The true risks are somewhat unclear, however, because cases without a classic presentation are less likely to be diagnosed and reported.

The primary objective of the ACIP in recommending Tdap for adolescents is to protect individual adolescents against pertussis while continuing the standard protection against tetanus and diphtheria [23]. An important secondary goal is to reduce the reservoir of pertussis within the population as a whole. This may be particularly important for infants. The recommendation for adults was put in place primarily to protect individual adults against pertussis and also to reduce the reservoir of pertussis [25]. Widespread immunization of adults may also reduce the impact of pertussis on healthcare facilities and other institutional settings.

The recommended timing of Tdap vaccination takes into account recommendations for the administration of other tetanus and/or diphtheria toxoid-containing vaccines, including MenACWY, because of an association between frequent doses of such vaccines and a risk of increased local and systemic reactogenicity [23].

HUMAN PAPILLOMAVIRUS

Recommendation for Adolescents: HPV vaccine is recommended for girls and boys 11 to 12 years of age and for older adolescents who have not yet been vaccinated. Children 9 to 10 years of age may also be vaccinated.

Recommendation for Adults: HPV vaccine is recommended for adults up to 26 years of age who have not completed the vaccine series. HPV vaccine is also recommended for those 27 to 45 years of age if desired or if a risk factor is present.

When it was first added, there was significant public controversy over the inclusion of the HPV vaccine on the adolescent immunization schedule. Some parents remain concerned about the vaccine's safety or about the possibility of promoting sexual activity among young teens. Meanwhile, in some places this vaccine is now required for school attendance, although exemptions are generally allowed [27].

Statistics regarding HPV infection and cancer illustrate the rationale behind the vaccine itself. About 13,820 cases of cervical cancer will be diagnosed in the United States in 2024, and more than 4,360 will die from the disease [28]. The CDC estimates that 46,700 cancers attributable to HPV occur each year, including (in order of frequency) cancer of the oropharynx, cervix, anus, vulva, penis, and vagina [16].

There is one HPV vaccine available in the United States: Gardasil 9, which is approved for use in individuals 9 to 45 years of age [12; 19; 113]. Cervarix was a bivalent vaccine covering HPV types 16 and 18; however, this vaccine is no longer available in the United States [12; 30]. Quadrivalent Gardasil (no longer available in the United States) was a quadrivalent vaccine covering types 6, 11, 16, and 18 [31]. In 2014, a 9-valent HPV recombinant vaccine (Gardasil 9) was approved for use in individuals 9 to 26 years of age and added protection to HPV types 31, 33, 45, 52, and 58 in addition to those types covered by the original Gardasil [108; 113]. In 2018, the FDA approved expanded use of Gardasil 9 to include women and men up to 45 years of age [113]. Three-fourths of cervical cancers are squamous cell tumors, and HPV 16 and 18 account for about 68% of these [32]. The rest are adenocarcinomas, and HPV types 16 and 18 account for about 83% of these tumors [32]. The increased coverage of the 9-valent vaccine has the potential to prevent up to 90% of oropharyngeal, cervical, anal, vulvar, penile, and vaginal cancers [108].

Epidemiologic data on HPV incidence and age of sexual debut suggest that the pre-teen years are an appropriate time to begin HPV protection [32]. Genital HPV is the most common sexually transmitted infection in the United States, with 13 million new infections among people ≥15 years of age each year [95]. Teens and young adults are particularly at risk; about half of those infections occur in individuals 15 to 24 years of age [32]. One multisite, clinic-based study of sexually active females found the highest prevalence of HPV in girls 14 to 19 years of age. In another study, using a representative, population-based sample, HPV prevalence was 26.9% among sexually active women 18 to 25 years of age [33]. The prevalence of types 16 or 18 was 7.8%. Another study, also intended to be representative of the general population, found that the prevalence of HPV was 26.8% for women 14 to 59 years of age and nearly 45% among women 20 to 24 years of age [34]. In the overall study population, the prevalence of type 16 was 1.5%, and type 18 was 0.8%.

An important consideration in protecting adolescents who are not yet sexually active is that HPV infection is common within the first few years after sexual debut [32]. In addition, studies have shown high antibody titers with vaccination at age 11 to 12 years. The projected impact of vaccinating girls at 12 years of age is a 20% to 66% reduction in lifetime cervical cancer risk, depending on the effectiveness of the vaccine and the duration of protection. Vaccination could also lead to a 21% reduction in low-grade abnormalities on Pap tests over the life of a cohort of vaccinated females. A comparison of HPV prevalence data from the vaccine era (2009–2012) and the prevaccine era (2003–2006) found that the prevalence of the HPV types included in the quadrivalent vaccine decreased by 64% (from 11.5% to 4.3%) among girls 14 to 19 years of age [17]. Considering the modest uptake of this vaccine, the potential impact is significant.

The recommendation to vaccinate young adults takes into account the fact that many will already be sexually active and may have been exposed to one or more types of HPV. Young adults who are not yet sexually active can receive the full benefit of vaccination. In addition, it is likely that many individuals who are infected have not yet encountered each of the vaccine-covered types, so they can receive at least partial benefit [35; 36]. The recommendation to vaccinate adults to the age of 26 years reflects the safety and efficacy testing on which the

initial vaccines' approvals were based [30; 31; 37]. Use in older individuals is also effective, and many patients will benefit from vaccination at 27 to 45 years of age. Medical professionals can inform patients of the option to receive the vaccine series or to complete the series, help assess the benefits and individual risk factors, and facilitate decision-making. As noted, the HPV vaccine remains significantly underutilized as of 2024.

ROTAVIRUS

Recommendation for Children: Rotavirus vaccine is recommended for infants 6 weeks to 14 weeks of age (maximum age for first dose: 14 weeks, 6 days). The last dose should be given by age 8 months, 0 days.

A rotavirus vaccine was first added to the immunization schedule in 1999 but was quickly taken off the market due to concerns about intussusception. The two available vaccines have each been tested in hundreds of thousands of infants [38; 39]. A large-scale study completed in 2014 found a slight increase in risk with RV5 (1.5 excess cases of intussusception per 100,000 recipients of the first dose) and some evidence of an elevated risk with RV1 [38]. However, these data should be considered in light of the benefits of vaccination. In an effort to maximize safety, these vaccines have a narrow age range for administration, reflecting the ages of the children in the large safety studies.

In adding rotavirus vaccination to the routine immunization schedule, the ACIP observed that rates of illness are similar in industrialized and less developed countries, suggesting that public health measures such as clean water supplies and good hygiene are not enough to control rotavirus disease [40]. Further, there is a high level of morbidity due to rotavirus in the United States in spite of available medical care. In the years before vaccination was available, rotavirus was responsible for approximately 20 to 60 deaths each year, 55,000 to 70,000 hospitalizations, more than 200,000 emergency department visits, 400,000 physician visits, and direct and indirect costs of approximately $1 billion [40; 41].

The vaccines are designed to mimic the effect of a first bout of rotavirus, which is usually the most serious [40]. Subsequent bouts of symptomatic infection can occur after a first natural infection, but they tend to be milder. As such, vaccination is not expected to prevent disease entirely but to reduce the severity of symptoms, the need for medical care, and the risk of serious sequelae, including hospitalization and death.

In 2009, the age parameters for vaccine administration were adjusted to harmonize the schedules of the two approved rotavirus vaccines [40]. One is a pentavalent reassortant vaccine based on a bovine rotavirus, often abbreviated as RV5. The other is a live, attenuated human rotavirus vaccine, often abbreviated as RV1. RV5 has a three-dose schedule, while RV1 requires two doses [41]. The maximum ages for these vaccines are somewhat different, according to their prescribing information, but an ACIP workgroup has concluded that safety and efficacy are unlikely to be affected if the same age limits are used for both [40].

MENINGOCOCCAL DISEASE

Recommendation for Children: MenACWY is recommended routinely for children 11 to 18 years of age, for older children who have not yet been vaccinated, and for children 6 weeks to 10 years of age in certain risk groups. MenB vaccination is recommended for children 10 to 18 years of age in certain risk groups. In addition, young adults 16 to 23 years of age (preferred age range: 16 to 18 years) may be vaccinated to provide short-term protection against most strains of serogroup B meningococcal disease.

Recommendation for Adults: MenACWY vaccine is recommended for adults 19 years of age and older with increased risk for meningococcal disease, including military recruits, freshmen college students living in dormitories, persons without a spleen or with a damaged spleen, those with terminal complement deficiency, and persons traveling to or residing in countries in which the disease is common. Revaccination with MenACWY every five years is recommended for adults previously vaccinated who remain at increased risk of infection. MenB vaccine is recommended for adults with certain risk factors, including all adults with anatomical or functional asplenia or persistent complement component deficiencies.

Historically, before widespread vaccination, there were about 1,400 to 2,800 cases of meningococcal disease in the United States each year [42]. Although not a common illness, meningococcal disease has a rapid course and a high degree of mortality, with a case-fatality ratio of about 10% to 14%. Among survivors, 11% to 19% will experience serious sequelae, such as neurologic deficit, deafness, or loss of a limb [43]. The degree of severity means that, in addition to putting the patient's life at risk, each case requires a substantial public health effort to identify additional cases quickly and prevent the disease from spreading [44].

There are two main types of serogroup A, C, W, and Y meningococcal vaccine: MenACWY and MPSV. However, MPSV is no longer available in the United States. The two available vaccines are MenACWY-TT (≥2 years) and MenACWY-CRM (≥2 months) [19; 45]. MenACWY vaccines cover serogroups C, Y, A, and W-135 [44]. In the United States, serogroups C, Y, and B have each been responsible for about one-third of cases overall.

Incidence of meningococcal disease also increases during adolescence, and this group is the main focus of the recommendations for vaccination with MenACWY. Among people 11 years of age and older, 75% of cases are caused by group C, Y, or W-135, which are all covered by the vaccine [42]. The original recommendation for the use of MenACWY focused on certain age groups: children 11 to 12 years of age, children entering high school, and college freshmen who would be living in dorms. These specifications were created because of concerns about there being a short supply of vaccine during the first few years of production [47]. Now that supply is expected to be adequate, the recommendation is to vaccinate all children 11 years of age and older who have not previously received vaccination against meningococcus, with a booster at 16 years of age. This broader recommendation is intended to simplify decisions about vaccinating and improve overall

coverage. The child and adolescent immunization schedules provide details about revaccinating children who have received MPSV in the past.

Creating a vaccine against serogroup B was particularly challenging because of its immunochemical structure. However, the first vaccine to protect against invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B was approved by the FDA in 2014 [46]. There are now two MenB vaccines available: MenB-FHbp and MenB-4C [18]. The MenB vaccines are approved for use in persons 10 to 25 years of age; however, because there is no theoretical difference in safety for persons older than 25 years of age compared to those in the approved age-group, MenB vaccine is recommended for use in persons older than 10 years of age who are at increased risk for serogroup B meningococcal disease, including situations and settings in which MCV would be appropriate [19]. MenB vaccine should either be administered as a three-dose series of MenB-FHbp or a two-dose series of MenB-4C. The two vaccines are not interchangeable; the same vaccine product must be used for all doses [18]. MenB vaccine may be administered concomitantly with an MCV vaccine but at a different anatomic site, if feasible [19].

In 2023, a pentavalent vaccine combining MenACWY and MenB coverage (termed MenABCWY) became available [120]. The MenABCWY vaccine consists of substance from MenB-fHbp and MenACWY-TT and is recommended as an option for people 10 years of age or older who are getting MenACWY and MenB vaccines at the same visit [120]. It is administered in two doses at least six months apart. If a patient receives MenABCWY vaccine, MenB-fHbp should be used for additional MenB dose(s) when MenACWY is not indicated; any MenACWY vaccine may be used for booster when given alone. The MenABCWY vaccine can be used only when both MenACWY and MenB vaccines are indicated at the same visit. Otherwise, MenACWY and MenB vaccines should be given separately as appropriate [120].

HEPATITIS A

Recommendation for Children: HepA is recommended for all children 12 to 23 months of age and for unvaccinated children 24 months and older (as catch-up vaccination).

Recommendation for Adults: HepA or combination HepA-HepB is recommended for certain risk groups, for those travelling to countries with endemic hepatitis A, and for those who desire protection (with no risk factor required for vaccination).

Hepatitis A can be a serious disease. According to U.S. surveillance data, an estimated 11% to 22% of people who contract hepatitis A are hospitalized [48]. Adults who are hospitalized lose an estimated 33 days of work, and those who do not require hospitalization lose about 15 days [48]. In the pre-vaccine era, infection was especially common among children. Although young children often had asymptomatic or unrecognized infection, they were an important source of disease transmission.

The ACIP has been pursuing an incremental strategy to increase immunization, with the goal of potentially eliminating indigenous hepatitis A virus transmission entirely [48]. At first, routine vaccination for healthy children was recommended only for areas with high rates of disease. Implementation of vaccination in such regions led to a decline in local disease rates to the lowest levels ever recorded. This left the highest rates in places where routine vaccination was not yet recommended. The next step was the current recommendation to vaccinate all children at 1 year of age [12]. (Some local programs also incorporate vaccination of older children.)

The range to begin routine vaccination, 12 to 23 months of age, was chosen in part because well-child visits are more frequent before 2 years of age. Vaccination is also recommended for older children and adults in certain high-risk groups. Younger children (6 to 12 months of age) may be vaccinated if they will be travelling internationally [12].

HERPES ZOSTER

Recommendation for Adults: RZV is recommended for individuals 50 years of age and older with no vaccination history and for individuals who previously received the ZVL vaccine. RZV is also recommended for individuals 19 years of age or older who are immunocompromised or who will be immunodeficient/immunosuppressed due to disease or therapy.

There are an estimated 1 million cases of herpes zoster each year, and incidence increases with age [49]. Without vaccination, about one-third of Americans will experience shingles at some point in their lives [49]. In addition to discomfort and inconvenience for the patient, there is also a risk of viral transmission leading to primary varicella in at-risk contacts. Postherpetic neuralgia (PHN) is an unfortunate but fairly common complication. A community-based study in Minnesota looked at the incidence of PHN as defined by various durations of pain [50]. Eighteen percent of patients experienced PHN-type pain for at least 30 days, 13% for at least 60 days, and 10% for at least 90 days [50]. The ACIP added the zoster vaccine to the adult immunization schedule to take advantage of the opportunity to decrease both the burden of disease and the risk of complications. In 2018, the recombinant zoster vaccine (RZV) was added as the preferred vaccine, and in 2020, the ZVL vaccine was discontinued [19]. RZV has better proven efficacy in preventing herpes zoster compared with ZVL, and breakthrough cases are associated with less severe herpes zoster-related pain and less interference on activities of daily living [56].

Although treatment for herpes zoster is available, it does not always fully alleviate symptoms [63]. In addition, the potential effectiveness of treatment initiated more than 72 hours after rash onset has not been established. When PHN occurs, treatments often have limited effectiveness, and tolerance in older patients may be poor. In a large clinical trial comparing RZV to placebo, the incidence of herpes zoster was reduced by 97.2% in vaccinated patients, and pain associated with shingles was substantially reduced [51]. The overall efficacy of

RZV against the incidence of of PHN (defined as persistent pain for 90 days) was 91.2%.

Of note, the zoster vaccine is recommended whether or not the patient has had a prior episode of shingles [19; 63]. Patients who previously received the ZVL vaccine should be revaccinated with RZV [19; 117]. Unlike the ZVL vaccine, RZV can be used in patients who have received the varicella vaccine and in those who are immunocompromised [117].

PNEUMOCOCCAL VACCINES

Recommendation for Children: PCV13 is recommended at 2, 4, 6, and 12 to 15 months of age. (PPSV23 is also recommended for certain risk groups at 2 years of age or older, with a single revaccination after 2 years.)

Recommendation for Adults: Pneumococcal vaccination (1 dose of PCV20 or 1 dose PCV15 followed by 1 dose PPSV23 at least one year later) is recommended for individuals 65 years of age and older and for younger adults in certain risk groups.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The ACIP recommends immunizing all adults 65 years of age or older who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown. One dose of PCV15 or PCV20 is given initially. If PCV15 is used, this should be followed by a dose of PPSV23 given at least one year after the PCV15 dose.

(https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf. Last accessed May 24, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

The pneumococcal conjugate vaccine recommended for routine use in healthy children, PCV13, covers 13 serotypes of *Streptococcus pneumoniae*. The use of this vaccine has led to a significant decline in IPD, from 98.7 cases per 100,000 children younger than 5 years of age in 1997–1999, to less than one case per 100,000 by 2007 and continuing to 2015 [2; 52]. Rates of all-cause pneumonia in children younger than 2 years of age have also declined, by about 35% between 1997 and 2006 with use of a vaccine covering seven serotypes [53]. Most of this decline occurred shortly after the vaccine became available.

However, the rates of non-PCV type IPD had been rising, and overall rates of IPD plateaued between 2002 and 2005 [52]. This prompted the development of the 13-valent pneumococcal conjugate vaccine, licensed in 2010. PCV13 includes coverage for six additional serotypes, which are responsible for a large proportion of remaining IPD [54]. Invasive pneumococcal disease caused by the 13 serotypes covered by PCV13 decreased from 91 cases per 100,000 people in 1998 to 0.56 cases per 100,000 people in 2021 [26].

Of note, PPSV, the 23-valent vaccine included on the adult immunization schedule, protects against 12 of the 13 serotypes in PCV13. PPSV23 can also be used in children and is recommended for certain risk groups, but it is not immunogenic in infants and very young children and is indicated for use only in people 2 years of age and older.

RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINATION

Recommendation for Infants: Within one week of birth, RSV immunization (one dose nirsevimab) should be administered to infants born in October through March whose mothers did not receive RSV vaccine, who received the vaccine less than 14 days prior to delivery, or whose RSV vaccination status is unknown. For infants born between April and September whose mothers fit these criteria, one dose nirsevimab should be administered shortly before the start of RSV season.

Recommendation for Adults: One dose RSV vaccine is recommended for all pregnant patients at 32 to 36 weeks' gestation from September through January in most of the continental United States, regardless of previous RSV infection. Based on shared clinical decision-making, one dose RSV vaccine may be administered to patients 60 years of age or older.

Starting in 2024, the immunization schedule includes recommendations for use of the RSV vaccines. Two RSV vaccines are available in the United States: Arexvy and Abrysvo. The strongest recommendation is for the use of RSV vaccination during pregnancy to prevent RSV lower respiratory tract infection in infants. Abrysvo is the only RSV recommended for use during pregnancy. All infants born to mothers who received RSV vaccine at least 14 days prior to delivery generally do not require immunization. However, infants born to mothers who did not receive the vaccine or whose vaccine status is unknown should receive nirsevimab immunization. In addition, infants with prolonged birth hospitalization discharged October through March should be immunized shortly before or promptly after discharge [121].

Vaccination with a single RSV vaccine dose has demonstrated moderate-to-high efficacy in preventing symptomatic RSV-associated lower respiratory tract disease among adults 60 years of age or older. In 2024, the ACIP added a recommendation for RSV vaccination for older adults based on shared clinical decision-making. Persons 60 years of age and older who are most likely to benefit from vaccination include those with chronic medical conditions (e.g., lung diseases, cardiovascular diseases, neurologic or neuromuscular conditions, kidney disorders, liver disorders, hematologic disorders, diabetes, and moderate or severe immune compromise); those who are considered to be frail; those of advanced age; those who reside in nursing homes or other long-term care facilities; and those with other underlying medical conditions or factors that a healthcare provider determines might increase the risk of severe respiratory disease [122].

In general, the timing of RSV vaccination is based on the seasonal patterns of RSV disease transmission. Providers in jurisdictions with RSV seasonality that differs from most of

HYPERSENSITIVIES AND VACCINE RECOMMENDATIONS		
Hypersensitivity	**Vaccine**	**CDC Recommendation**
Yeast	HPV HepB PCV13	Do not use
Latex	Rotavirus (RV1), MenB	Check packaging to see if latex is used and for guidance
Gelatin	MMR Varicella	Use extreme caution if administering
Neomycin	IPV MMR Varicella HepA Some influenza vaccines	Do not use
Streptomycin	IPV	Do not use
Polymyxin B	IPV Some influenza vaccines	Do not use
Thimerosal	Some brands/formulations, including certain DTaP, influenza (IIV), Td, DT	Check package insert
Source: [20; 29]		*Table 6*

the continental United States (e.g., Alaska, tropical climates) should follow guidance from public health authorities or regional medical centers on timing of administration based on local RSV seasonality [12; 19].

VACCINE CONTRAINDICATIONS

GENERAL INFORMATION

Confusion about contraindications can lead to undervaccination or, occasionally, to serious adverse events if contraindicated vaccines are given. There are a few general safety considerations that apply to all vaccines. There are also several situations in which healthcare professionals may hesitate to administer vaccines, when in fact most could be given with a high degree of safety.

As a general rule, a serious allergic reaction to a prior dose or a severe allergy to any vaccine component is a contraindication to the use of any vaccine; however, mild or moderate allergy to a vaccine component is not considered to be a contraindication [55]. In most cases, vaccination should be deferred in the setting of moderate or severe acute illness.

On the other hand, vaccination is generally not contraindicated in the following situations [55]:

- Mild acute illness, with or without low-grade fever, or recovering from illness
- Lack of previous physical examination in well-appearing person
- Current use of antimicrobial therapy (except certain antivirals with VAR and zoster)
- Premature birth (except HepB in certain circumstances)
- Recent exposure to infectious disease
- History of non-vaccine allergy
- Current use of allergen extract immunotherapy
- History of Guillain-Barré syndrome (GBS)

The prescribing information for VAR does note a small possibility of transmission of vaccine virus to healthy susceptible contacts (including pregnant women if they are susceptible to varicella) and recommends weighing this small risk against the risk of acquiring and transmitting natural varicella virus [57].

The following details about specific contraindications and cautions are based primarily on recommendations from the CDC. The CDC reports and current prescribing information should always be consulted.

ALLERGY/HYPERSENSITIVITY

The ingredients, contraindications, and precautions for any vaccine should be reviewed before administering it to a patient with known allergies or a history of a severe reaction to a previous dose or to any vaccine ingredient. However, clinicians can be well served by recalling many of the potential hypersensitivities. ***Table 6*** is based on a list of contraindications and cautions as recommended by the CDC, which provides recommendations when anaphylactic allergy is present [55]. (A fully definitive list is beyond the scope of this course. For a comprehensive list, visit https://www.vaccinesafety.edu/components.)

IMMUNODEFICIENCY

Immunodeficiency creates a potentially confusing situation regarding vaccination, because there are different degrees and causes of immune suppression. In general, the CDC recommends that MMR, varicella, and LAIV, which contain live virus, should not be used [55]. The prescribing information for LAIV notes that administration to immunocompromised patients requires careful weighing of benefits and risks [22]. If the patient is healthy but there is a close contact who is severely immunosuppressed and requires care in a protective environment, IIV4 is preferred over LAIV [55].

VAR also contains live virus. According to the CDC, it is contraindicated in patients with cellular immunodeficiencies but may be used in patients with impaired humoral immunity [55]. The prescribing information, however, includes hypogammaglobulinemic and dysgammaglobulinemic states as contraindications [57]. If a first-degree relative has congenital or hereditary immunodeficiency, VAR should not be given unless the patient's own immune competence has been verified [57; 59]. For such patients, the prescribing information for MMR notes that it, too, should also be deferred until immune competence is confirmed [60]. According to the prescribing information for VAR, because there may be rare transmission of the vaccine virus between recipients and susceptible contacts, recipients should try to avoid contact with susceptible, high-risk contacts for up to six weeks [57]. This includes immunocompromised persons and pregnant women if they are susceptible to chickenpox. (If contact is unavoidable, vaccination risk should be weighed against the risk of acquiring and transmitting natural varicella virus.)

Unlike the ZVL vaccine, which was contraindicated in most immunodeficient individuals, RZV is considered safe and is recommended for patients with immunodeficiency. According to the ACIP, RZV should be administered to adults 19 years of age or older who are or will be at increased risk for herpes zoster due to immunodeficiency or immunosuppression caused by known disease or therapy [58; 117].

The safety and efficacy of the rotavirus vaccines have not been established in patients who are immunosuppressed. In such patients, the ACIP recommendation is to consult with an infectious disease specialist or immunologist before giving the vaccine [40]. In phase 3 studies of RV5, viral shedding was observed as long as 15 days after a dose, raising concerns about use in patients with immunosuppressed contacts [61]. However, the actual risk of transmission is unknown. RV1 can also be shed after a dose, with shedding tending to peak at about seven days [62]. Again, the risk of transmission is not known.

Many vaccines may be less immunogenic in patients who are immunosuppressed. Potential effectiveness, as well as timing in patients taking immunosuppressive therapy, should be considered.

PREGNANCY

A few of the routine vaccines for healthy persons are contraindicated in pregnancy. MMR and VAR should not be used, and the CDC recommends against the use of LAIV [55]. The zoster vaccine should also be delayed, although the ACIP makes no recommendation for use during pregnancy [58]. For many other vaccines, safety during pregnancy is unknown. For example, there is little safety data on MCV and HPV vaccines when used in pregnant women, although caution is indicated with HPV [32; 42; 48; 55]. If Td or Tdap is to be given, administration during the second or third trimester is preferred. For many vaccines without good pregnancy data, providers are encouraged to report any exposure to the vaccine in a pregnant woman to the manufacturer's pregnancy registry; details are provided in the prescribing information.

In general, prescribing information should be consulted for recommendations regarding individual vaccines and pregnancy, and risks and benefits reviewed with the patient as necessary.

TUBERCULOSIS

While a positive purified protein derivative (PPD) test on its own is not generally a contraindication to vaccination, some vaccines should not be used in the presence of active, untreated tuberculosis. In such cases, MMR should not be given, due to a theoretical risk of exacerbating the disease [55].

HISTORY OF GUILLAIN-BARRÉ SYNDROME

Some vaccines have been associated with Guillain-Barré syndrome (GBS), although it is often unclear whether the vaccines actually cause this syndrome [55]. This section will summarize contraindications of routine vaccines for healthy children and adults with a history of GBS; more information about certain vaccines and GBS is included in the section on vaccine safety.

DTaP, Tdap, and Td all require caution if GBS occurred in a patient within six weeks after a previous dose of a vaccine containing tetanus toxoid [21; 23; 64; 65]. Similarly, IIV/RIV requires caution if GBS occurred within six weeks of a prior influenza vaccination, and the CDC suggests considering not vaccinating such patients if they are not at high risk of influenza complications [21; 64]. The prescribing information for LAIV recommends caution in any patient with a history of GBS, and the ACIP has identified history of GBS after an influenza vaccination as a contraindication [21; 22]. The actual risks with these or other vaccines are not known, and providers should weigh the potential risk of vaccinating against the patient's risk of serious illness.

OTHER ISSUES

There are several other concerns or cautions with specific vaccines. Although it is not possible to list every issue here, a few of the specific contraindications will be discussed.

Rotavirus Vaccine and Gastrointestinal Disease

Some studies have suggested a small increase in the risk of intussusception following rotavirus vaccination [38; 66]. In patients with a history of intussusception, benefits and risks should be weighed on an individual basis.

DTaP, Tdap, and Neurologic Events

Both DTaP and Tdap are contraindicated if encephalopathy occurred within seven days of a prior dose of a vaccine with pertussis components [23; 25; 55]. This is based on a possible link between DTP and encephalopathy and evidence suggesting an association between acellular pertussis vaccines and encephalopathy in Japan (about one attributable case per 10 million doses). Canadian surveillance data from 1993 to 2002, on the other hand, did not find a link between whole-cell or acellular pertussis vaccines and acute encephalopathy cases. Contraindications and precautions listed in the prescribing information for vaccines with pertussis components also include the presence of unstable or evolving neurologic disorders, and package inserts and the ACIP recommendations should be reviewed for details [67; 68; 69; 70; 71; 72]. The CDC recommends that decisions about DTaP in children with proven or suspected neurologic conditions be decided on an individual basis [55].

With DTaP, caution should also be observed if reactions after a prior dose included events such as high fever, collapse or shock-like state, or persistent/inconsolable crying lasting three hours or more within two days of prior dose, or seizure within three days [23; 25; 55]. However, according to the ACIP recommendations, such reactions following DTP or DTaP should not be considered contraindications to use of Tdap or Td in adolescents and adults.

Of note, the prescribing information for some, but not all, tetanus toxoid-containing vaccines does caution against use in patients who have had neurologic reactions following a previous dose of Td or of tetanus toxoid.

DTaP, Tdap, Td, and Arthus Reactions

History of an Arthus reaction is another consideration with tetanus toxoid-containing or diphtheria toxoid-containing vaccines [23; 25; 55]. An Arthus reaction is a local vasculitis that is associated with an immune reaction. Although it is an uncommonly reported event after vaccination, it can occur with vaccines containing tetanus or diphtheria toxoid. Signs include swelling, induration, edema, and hemorrhage, and there may be local necrosis. Pain is severe. The CDC recommends that, in a patient who experienced an Arthus reaction after a prior dose of tetanus toxoid- or diphtheria toxoid-containing vaccine, providers should consider deferring doses of DTaP, Tdap, or Td for at least 10 years [55]. If the reaction was to a vaccine with diphtheria toxoid but not tetanus toxoid, and more than 10 years have elapsed since tetanus vaccination, the patient can be evaluated for serum antitetanus level to determine if tetanus protection is needed before vaccination is considered.

Vaccines Containing Diphtheria or Tetanus Components

Certain vaccines contain diphtheria or tetanus components, although they are indicated for prevention of other diseases. For example, MCV and PCV contain a diphtheria component (but no tetanus toxoid) and therefore should be avoided in patients with hypersensitivity to diphtheria toxoid [73; 74]. In MCV, *Neisseria meningitides* capsular proteins are conjugated to diphtheria toxoid protein. In PCV, capsular antigens of *Streptococcus pneumoniae* are conjugated to diphtheria CRM197 protein. Certain Hib vaccines contain a *Haemophilus influenzae* capsular polysaccharide bound to a tetanus toxoid [75]. As always, vaccine components should be reviewed in patients who have known hypersensitivities or have had serious reactions to prior vaccinations.

Influenza (LAIV) and Acute or Chronic Illness

The ACIP recommends that LAIV not be used in patients with asthma or other conditions predisposing to flu complications [12; 21]. In most cases, IIV or another type can be used instead. LAIV should also be avoided in children and adolescents who are receiving aspirin or salicylate therapy. Acute respiratory illness with nasal congestion, which could interfere with delivery of the vaccine, is a reason to consider delaying the use of this vaccine until the congestion has decreased. Children younger than 5 years of age who have recent or recurrent wheezing should not receive LAIV [12; 21].

PPSV Considerations

According to the prescribing information, PPSV should be deferred in patients with febrile respiratory illness or other active infection, unless the benefit of vaccinating at that time outweighs the risk [76]. Some providers revaccinate with PPSV every five years. However, revaccination is not recommended in most healthy patients [77]. Most adults will need one lifetime dose. A second dose should be given to patients who are 65 years of age and older if they were previously vaccinated with PPSV prior to 65 years of age and if more than five years have passed [19]. Children and adults at very high risk of serious pneumococcal disease or who are likely to have a rapid decline in antibody levels (such as those with anatomic or functional asplenia or who are immunocompromised) should also receive a second dose at least five years after the first [19].

VACCINE SAFETY

Vaccine safety is initially established through clinical trials, and benefits must be shown to outweigh any risks before a new vaccine can be approved. However, the trial populations are not necessarily large enough to ensure that all possible adverse events are observed. Postmarketing surveillance provides additional safety information.

In the United States, vaccine safety is monitored through three major systems. The Vaccine Adverse Event Reporting System (VAERS) invites voluntary reporting [80]. VAERS receives approximately 30,000 reports annually, with most reports coming from vaccine manufacturers and healthcare providers. Approximately 20% of reports relate to storage and handling of vaccines, and about 85% to 90% of the reports relating to vaccine reactions describe mild side effects such as fever, arm soreness, and crying or mild irritability. Reporting forms are available at the VAERS website, https://vaers.hhs.gov. This type of surveillance is a useful way to collect information about possible adverse events, particularly uncommon events.

However, with no control group, it is often difficult to be certain whether reported events are truly related to vaccination. Researchers often compare reported events to background rates of disease, but because reporting is voluntary (referred to as passive reporting), it is not possible to know the true number of events. VAERS therefore serves primarily as an "early warning system," alerting the CDC to potential problems that require further investigation.

The Vaccine Safety Datalink (VSD) is a collaborative project, partnering the CDC with nine large managed-care organizations [81]. Each managed-care organization tracks and reports data about vaccinations given, medical outcomes, and patient demographics. The VSD project is designed to allow planned safety studies and rapid investigations of concerns raised by patterns in VAERS data or other sources.

The Clinical Immunization Safety Assessment (CISA) Project is a network of vaccine safety experts from the CDC's Immunization Safety Office, seven medical research centers, and other partners [82]. Researchers at these centers evaluate and investigate questions about health risks that may be associated with immunization.

Safety information about several specific vaccines is discussed below, with an emphasis on issues that have been in the news and may thus be on patients' or parents' minds.

MMR AND AUTISM

Although measles was considered effectively eliminated in the United States in 2000, resurgence in the disease and regional outbreaks have resulted from suboptimal vaccination rates. In 2014, there were 667 cases of measles in the United States, more than 10 times the number of cases in 2000; another even larger spike occurred in 2019 (1,282 cases in 31 states) [6]. A large outbreak in 2014–2015 was linked to unvaccinated children visiting Disneyland, the source patient probably being infected overseas (likely the Philippines) [6]. The decrease in vaccine coverage is in part attributed to the false belief that the MMR vaccine may cause autism. Based on multiple studies, experts generally agree that there is no evidence for a link between the MMR vaccine and autism, and it is important that clinicians address these misconceptions with patients. In 2004, the Institute of Medicine (IOM) reported that "the body of epidemiological evidence favors rejection of a causal relationship between the MMR vaccine and autism" [83]. The American Academy of Pediatrics has also concluded that the evidence does not support such a connection. In addition, autism is not thought to be immune-mediated, and there is no clear mechanism by which MMR would cause this disorder [84].

Research on the topic includes a Canadian study involving 27,749 children born between 1987 and 1998 [85]. This study found no association between rates of pervasive developmental disorder and either one or two doses of the MMR vaccine. In a 2015 retrospective cohort study of 95,727 children, MMR vaccine receipt was not found to predict autism diagnosis, even among children with older siblings with an autism spectrum disorder [78]. A study of 657,461 children born in Denmark between 1999 and 2010 found no increased risk of autism in those who received the MMR vaccine, including in special subgroups (e.g., autism risk factors, other childhood vaccinations) [115].

Some of the concern about MMR and autism is based on a study in the late 1990s that found measles virus ribonucleic acid (RNA) in the gastrointestinal tissue of children with gastrointestinal problems and autism. However, a case-control study designed to explore this issue further found no association between autism and persistent measles virus RNA in the gastrointestinal tract, or between autism and MMR exposure [86].

Another study used polymerase chain reaction to detect measles virus nucleic acids in the peripheral blood mononuclear cells of children with autism spectrum disorder [87]. This study found no evidence of measles virus persistence in affected children.

THIMEROSAL AND AUTISM

Some of the concerns about autism involve the use of thimerosal, a mercury-containing preservative. The IOM has concluded that, as with concerns about MMR, the evidence favors rejecting the idea of a causal relationship between thimerosal-containing vaccines and autism [83]. In addition, the same study that looked at MMR and autism in a large cohort of Canadian children also looked for any relationship between ethylmercury exposure and autism and failed to find a connection [85]. Exposure levels were comparable to levels in the United States during the 1990s. Another study, which examined the incidence of autism in California children before and after thimerosal was removed from childhood vaccines, found no decrease in autism following the change [88].

Most vaccines for children 6 years of age or younger that had contained thimerosal either no longer contain this preservative or contain only trace amounts—small enough that the FDA considers them "preservative free" [89]. IIV vaccines are now largely in this category, as "preservative-free" preparations of IIV are widely available. For the 2023–2024 season, 91% of IIV vaccines are thimerosal-free or thimerosal-reduced formulations [118].

MULTIPLE VACCINES AND THE IMMUNE SYSTEM

Some parents worry that receiving multiple vaccines at a single visit is hard on a child's immune system or that it will weaken the child's immune defenses. However, there is no evidence that giving multiple vaccinations at a single visit weakens the immune system [84]. In addition, although more childhood vaccines are given than in the past, the immunologic load has actually decreased due to advances in vaccine technology [84].

ROTAVIRUS VACCINES AND INTUSSUSCEPTION

Parents and physicians who remember the withdrawal of the original rotavirus vaccine may worry about a risk of intussusception. Each of the current rotavirus vaccines has been tested in large safety studies.

Safety testing for RV5 included the Rotavirus Efficacy and Safety Trial, involving more than 68,000 infants [90]. However, postlicensure data from the Mini-Sentinel program for 2004–2011 indicate a slightly increased risk of intussusception after the first dose (but not after subsequent doses) [38]. Prelicensure clinical trials did raise the possibility of Kawasaki disease as an uncommon adverse event, with five cases seen in infants who received the vaccine and one case in a child who received placebo (a non-significant difference) [40]. There have been a few cases reported since licensure, but these are not thought to exceed the background rate [91].

Original studies with RV1 involved more than 63,000 infants [39]. Again, no association with intussusception was observed. Since then, a major study in the United States did note a possibly increased risk of intussusception [38]. According to the CDC, there is a 1 in 20,000 to 1 in 100,000 risk of intussusception from either rotavirus vaccine [92]. Composite safety data have shown numerically higher cases of Kawasaki disease with the vaccine than with placebo, but again this was not a statistically significant difference [62].

INFLUENZA VACCINE AND GUILLAIN-BARRÉ SYNDROME

GBS was associated with a swine flu vaccine in 1976, with an estimated 1 case per 100,000 people vaccinated [21]. Some observational studies since then have found a small increase in GBS cases associated with influenza vaccination, while others have found no link. Whether there is an association between current influenza vaccines and GBS is not known. According to the CDC, based on studies in prior seasons, if an association does exist the risk would likely be low (i.e., one case per 1 million people vaccinated). The IOM conducted a thorough scientific review of this issue in 2003 and concluded that people who received the 1976 swine influenza vaccine had an increased risk for developing GBS. Scientists have multiple theories regarding why this increased risk may have occurred, but the exact reason for this association remains unknown [93].

MCV AND GUILLAIN-BARRÉ SYNDROME

As of early 2008, there had been 26 confirmed case reports of GBS within six weeks of vaccination with MenACWY-D [94]. This is likely similar to the background rate, and causality has not been established. However, the CDC and the FDA have noted that the timing in relation to vaccination was reason to pursue the question further and to gather more information. Two large studies were conducted to determine if MenACWY-D was the cause of GBS in pre-teens and teenagers, but no link was found among 21 million vaccinated individuals [94; 119]. The other MenACWY vaccines are also not associated with GBS.

Providers are asked to report any cases of GBS that coincide with vaccination to VAERS. Providers are also asked to report all GBS cases to their state health departments, in accordance with local guidelines. More complete data collection will help to clarify whether GBS is a concern with these vaccines.

HPV VACCINE AND ADVERSE EVENTS

Clinical trials and the post-licensure monitoring data of three HPV vaccines (two discontinued and one in current use) show that they are safe [107]. Since the licensure of the HPV vaccines, both the CDC and the FDA have monitored HPV vaccine safety through VAERS, VSD, and CISA systems. It should be noted that most of the available data is from the quadrivalent Gardasil formulation, which is no longer available in the United States. A 2009 CDC/FDA report found that the most common adverse events reported to VAERS following vaccination with Gardasil were fainting, swelling at the injection site, headache, and nausea. Seven percent were considered serious. However, no common pattern for serious events has emerged, making it difficult to form theories about causality. GBS was reported but did not appear to occur at a rate above background levels. Blood clots were reported in a small number of patients, most of whom had pre-existing risk factors (e.g., smoking, obesity, use of oral contraceptives). Over the first three years of its use, more than 28 million doses of Gardasil 9 were administered, and 7,244 adverse events were reported to VAERS, of which 3% (217 events) were classified as serious [107].

VSD surveillance examined adverse events associated with administration of Gardasil (e.g., GBS, stroke, venous thromboembolism) and found no statistically significant increased risk for any of these adverse events [79]. Ongoing safety studies for HPV include review of serious individual reports to VAERS; VAERS data reviews by the FDA; review of two years of safety data on Gardasil used in boys and men; research on venous thromboembolism following HPV vaccination; and continued consultation with CISA [107].

Because of postmarketing reports, the prescribing information for the HPV vaccines includes a warning that syncope, sometimes associated with seizure-like activity, has been reported following vaccination [107]. Patients should be observed for 15 minutes following injection.

OVERCOMING BARRIERS FOR CHILDREN AND ADOLESCENTS

Barriers to on-time vaccination among children and adolescents can be traced to many different issues, including parental concerns, the need for multiple visits, cultural differences, and financial constraints. Some parents are uncomfortable with the idea of multiple shots given at a single visit, and some have safety concerns that lead them to forgo certain vaccinations for their children or refuse immunization entirely. In some cases, parents are simply unaware of their children's preventive care needs.

EDUCATING PARENTS ABOUT VACCINES AND VACCINE SAFETY

In the last decade, news reports and social media misinformation have increased parents' concerns about vaccine safety and

have led some parents to reconsider the value of immunization. Although certain vaccinations are required for school attendance, parents can usually opt out for religious reasons. Some states allow "philosophical" objections as well, creating room for parents who feel uneasy about childhood vaccinations to avoid them. In places where requirements are stricter, some parents are choosing to home school their children rather than accept vaccination [96].

Healthcare providers can have an influence when parents are concerned or confused about vaccines. For example, in one survey, 28% of parents had some level of uncertainly about vaccines [97]. For those who ultimately decided to allow timely vaccination, assurances or information provided by a healthcare provider were important reasons for the decision.

When explaining vaccine recommendations or vaccine safety, the provider should take into account the parents' level of health literacy, any language or reading literacy barriers, and social and cultural expectations. For example, for some parents, written material may not be sufficient due either to a low level of literacy or to a desire to discuss the information with the physician directly.

Because patient education is such a vital aspect of vaccine promotion, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. 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.

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/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.

REDUCING THE NUMBER OF INJECTIONS

Many parents are upset by the idea of multiple shots on a single visit, feeling that their children will be too frightened or upset. Some parents request that certain shots be delayed, and some providers have devised alternative immunization schedules that spread injections out over time. However, there is evidence that delaying vaccinations to reduce the number of injections can lead to undervaccination. When doses are deferred, immunization coverage at both 1 and 2 years of age declines [98]. Future visits may be missed or delayed, and children may be left vulnerable to vaccine-preventable illnesses.

One way to help reduce the number of injections is to make use of combination formulations, which allow for multiple vaccines in one shot [99]. In addition to the familiar MMR and DTaP, Tdap, and Td vaccines, available combination products include [12; 19]:

- HepA and HepB (adults only)
- DTaP and IPV
- DTaP, IPV, and HepB
- DTaP, IPV, and Hib
- DTaP, IPV, Hib, and HepB
- MMR and varicella
- MenACWY and MenB

Some of these products include premixed components, while others involve components that must be combined by the healthcare provider according to instructions. Except for products that are designed to be used in this manner, individual vaccines should not be combined in a single syringe.

In their 2024 General Recommendations on Immunization, the ACIP recommended the use of combination vaccines whenever possible to reduce the number of injections and improve coverage [100]. The 2024 immunization schedule includes these formulations as an option when any component of the combination is indicated, other components are not contraindicated, and the combination vaccine is FDA approved for that dose of the series [12].

ADDRESSING CONCERNS ABOUT VACCINE COSTS

The Vaccines for Children (VFC) program is designed to help overcome cost as a barrier to childhood vaccination. All of the ACIP-recommended vaccines are available for children enrolled in Medicaid, with VFC covering children through 18 years of age [101]. Children who have no health insurance coverage, children who are underinsured, and children who are American Indian or Alaska Native are also eligible for vaccines through VFC.

"Underinsured" children are those who have private health insurance coverage that does not include vaccines, that covers only certain vaccines, or that has a cap on the amount to be paid for vaccinations [101]. In each case, VFC will cover vaccines that the insurance does not. These children must visit a Federally Qualified Health Center (FQHC) or Rural Health Clinic (RHC) to receive the covered vaccines. An FHQC is a center with a special government designation to provide care to an underserved population. A typical FQHC would be a community health center in an underserved area. An RHC is a specially certified clinic in an underserved area or one where there is a recognized shortage of healthcare professionals [101]. All other children may receive vaccines from any enrolled VFC Program provider; most physicians, clinics, hospitals, public health clinics, community health clinics, and some schools are VFC Program providers.

Although the vaccines are free and patients cannot be charged for them, providers participating in VFC may charge an administrative fee to cover other costs [101]. These fees are established by the states. Healthcare providers can learn more about VFC, including how to become a VFC provider, at the Vaccines for Children Program website, https://www.cdc.gov/vaccines/programs/vfc/index.html.

INSTITUTING REMINDER SYSTEMS

Reminding parents to bring their children in for vaccinations is a proven way to increase coverage and is recommended in standards developed by the National Vaccine Advisory Committee and supported by other organizations [102; 103]. Reminders need not take up extensive staff time. Mailed reminders have been shown to increase child vaccination rates and so have telephone calls, which may be computer-generated to save work by the office staff [104; 105; 106]. Outreach should be more intensive for families at high risk of missing appointments [102].

Setting up a system of reminders for the physician who is responsible for prescribing the vaccinations can also be helpful. Charts can be flagged, or a computerized database can be used. The National Vaccine Advisory Committee also recommends conducting chart audits to review how well the practice is meeting immunization needs and to look for areas for improvement [102].

OVERCOMING BARRIERS FOR ADULTS

Barriers to adult vaccination are similar to those impacting children and adolescents. These include: cultural differences, lack of information about what vaccinations are needed and when, lack of physician recommendation, unawareness that the protection they received as children for some diseases decreases over time, unawareness of vaccines received in childhood, lack of insurance, and mismanagement of time/priorities during office visits.

Lack of awareness is a primary reason that adults miss recommended vaccinations. It is common for adults to report that no healthcare provider had recommended a given vaccination, and so they did not know it was needed. There may also be cultural differences in how adults approach vaccination or in how services are provided. According to 2021 surveillance data, racial/ethnic disparities exist for all seven vaccines the CDC is tracking [7]. The gap is most marked for black adults, whose vaccination rate averaged 18% lower than their white counterparts with respect to seasonal influenza, tetanus (with pertussis), pneumococcal, herpes zoster, and hepatitis B [7].

"Missed opportunities," visits during which a patient was eligible for a vaccination but did not receive it, are common for adults. Reasons include constraints on time during office visits, a focus on acute care needs instead of prevention, and a lack of standing orders or an office reminder system that could prompt staff to offer the recommended vaccines [109; 110].

REDUCING "MISSED OPPORTUNITIES" FOR ADULTS

There is evidence that when physicians recommend preventive services, patients are interested in receiving them. For example, 95.1% of patients in a national survey stated that they would accept the herpes zoster vaccination if their doctor recommended it [111]. Standards provided by the National Vaccine Advisory Committee, in cooperation with more than 60 organizations, offer evidence-based methods to help reduce missed opportunities for adults [110]. Providers should assess the vaccination status of all new patients and review vaccination status annually. Pneumococcal vaccination status should be reviewed when patients present for influenza vaccination.

Standing orders for vaccination should be used, based on evidence that they improve adult vaccination coverage in many different settings [110]. Reminder systems for staff can also improve vaccination rates. In one review of studies, use of physician reminder systems, such as chart notations, stickers, and patient lists, improved coverage by a median of 22% [112]. Assessing a practice's success at vaccinating patients who are eligible and reporting the results to staff can also help to improve coverage [110].

REMINDER SYSTEMS FOR ADULT PATIENTS

Telephone calls, mailed reminders, and texts/electronic reminders can help raise vaccination coverage among adults as well as among children [110]. Reminders can specify that patients are due or overdue for vaccinations, or they can invite patients to contact the provider's office to see which vaccinations they need. As with children, adults who are likely to miss appointments or fail to comply with recommendations may need particularly intensive follow-up.

CONCLUSION

Staying up-to-date, working with patients to maximize vaccination coverage, and monitoring and improving day-to-day practice can all help to improve vaccination rates. However, keeping up with changes to the child, adolescent, and adult immunization schedules can be challenging. Annual schedules often change from year to year and include both major changes and subtle ones. Mid-year announcements from the CDC and the ACIP require clinicians to be alert to new information and to make adjustments to practice. To help clinicians check for updates, verify information about vaccines, and locate answers to common clinical questions, the CDC provides a Vaccines and Immunizations website, as does the Immunization Action Coalition. Healthcare professionals should consider every healthcare visit as an opportunity to assess vaccination status and administer vaccines when needed. This will improve rates across the life spectrum, from infancy to elderly.

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COURSE TEST - #91743 CHILD, ADOLESCENT, AND ADULT IMMUNIZATION SCHEDULES

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.

This 5 Hour activity must be completed by February 28, 2026.

1. In the United States, what group is responsible for regulating vaccines?
- A) *Centers for Disease Control and Prevention*
- B) *Advisory Committee on Immunization Practices*
- C) *FDA Center for Biologics Evaluation and Research*
- D) *FDA Vaccines and Related Biological Products Advisory Committee*

2. According to the 2024 immunization schedule, what are the recommended vaccine doses for a healthy, 2-month-old infant born in June with no special risks or contraindications who is up-to-date on vaccinations so far?
- A) *DTaP, Hib, IPV, and HepB if needed*
- B) *DTaP, Hib, PCV, IPV, and HepB if needed*
- C) *Rotavirus, DTaP, Hib, IPV, and HepB if needed*
- D) *Rotavirus, DTaP, Hib, PCV13, IPV, and HepB if needed*

3. Assuming no special risk groups or contra-indications and assuming that the ACIP recommendations are followed, what vaccines would a male patient, 50 years of age, be likely to receive?
- A) *Tdap or Td only*
- B) *Tdap or Td, IIV, and zoster*
- C) *Tdap or Td, IIV, and PPSV23*
- D) *Tdap or Td, IIV, zoster, and PPSV23*

4. The ACIP rationale for expanding the recommendation for influenza vaccination to include all children from 6 months to 18 years of age includes
- A) *adolescents typically have high rates of physician visits.*
- B) *universal childhood vaccination is expected to help increase coverage for at-risk groups.*
- C) *missed school days due to influenza have been low but proven to adversely affect children's grades.*
- D) *a large new clinical trial reinforced confidence in the safety and efficacy of influenza vaccination in school-age children.*

5. According to the ACIP recommendations, and considering healthy patients without special risk factors or contraindications, who should receive the HPV vaccine?
- A) *Girls 11 to 12 years of age, plus adult women at high risk of contracting HPV*
- B) *Girls 15 years of age or older, plus adult women at high risk of contracting HPV*
- C) *Girls younger than 18 years of age who are sexually active, plus adult women through age 26 who have not been vaccinated*
- D) *All individuals 11 to 26 years of age who have not been vaccinated*

6. The ACIP rationale for recommending HPV vaccination to preteens includes all of the following, EXCEPT:
- A) *HPV infection is particularly common in teenagers and young adults.*
- B) *Vaccination before the age of sexual debut is likely to offer the most benefit.*
- C) *Infection with HPV often occurs within the first few years after sexual debut.*
- D) *After an individual has been infected with any type of HPV, the vaccine is no longer of benefit.*

7. What change was made to the recommendations regarding vaccination against rotavirus in 2009?
- A) *Three rotavirus vaccines are now available.*
- B) *Ages for dosing were harmonized for the two available vaccines.*
- C) *The number of doses was standardized, with both vaccines now requiring 2 doses.*
- D) *The age to initiate rotavirus vaccination was expanded to include infants up to 1 year of age.*

8. Why is MCV included as a routine vaccination for healthy children?

A) *Unlike MPSV, MCV covers all of the most common meningococcal serotypes.*
B) *The high number of cases, about 45,000 in the United States each year, makes vaccination essential.*
C) *Vaccinating children protects them against meningococcal disease in middle age, when incidence becomes highest.*
D) *In addition to the high case-fatality rate, each case of meningococcal disease requires substantial resources to identify additional cases and prevent disease spread.*

9. The zoster vaccine is included on the adult immunization schedule. The recommendation for this vaccine includes

A) *adults 50 years of age and older.*
B) *adults 65 years of age and older.*
C) *only adults with certain medical risk factors.*
D) *only adults who have never had chickenpox.*

10. Before vaccination was available, what proportion of the population experienced herpes zoster at some point in their lives?

A) *About one-tenth*
B) *About one-third*
C) *About one-half*
D) *About two-thirds*

11. If a patient has a severe (anaphylactic) latex allergy, how would this affect the vaccinations he or she could receive?

A) *No vaccinations should be given.*
B) *Some vaccines would be contraindicated.*
C) *All vaccines can be used, but 15 minutes of observation is recommended.*
D) *There would be no change, because latex is not used in manufacturing vaccines.*

12. A father brings his 5-year-old son, Patient S, in for a checkup one morning in November. He states that Patient S has had "the sniffles" for the past two days and that he has been " running a bit of a fever." On exam, Patient S appears well except for nasal congestion. His temperature is 99.0°F. Patient S's medical history is unremarkable, he has no known allergies, and he tolerated his previous vaccinations well. He was up-to-date on all recommended vaccinations through 2 years of age, but has not received any vaccinations since then. At today's visit, which of the following vaccines should probably be deferred?

A) *IPV*
B) *DTaP*
C) *MMR*
D) *LAIV*

13. A mother brings her young daughter to a new pediatrician for the first time. She is changing doctors because her previous pediatrician refuses to see patients whose parents decline to have them vaccinated. She explains, "I know that MMR vaccine can cause autism, and I don't want that to happen to my child." What can you tell her?

A) *Large observational studies have failed to find a link between MMR and autism.*
B) *Experts do not believe that MMR causes autism, but this issue has not been studied.*
C) *An older type of MMR was a cause of autism, but this specific vaccine is no longer used.*
D) *Good evidence links MMR and autism, but the benefits of vaccination are considered to outweigh the risks.*

14. Some parents have concerns about the presence of thimerosal in childhood vaccines. Which of the following is correct?

A) *Experts believe that thimerosal does not cause autism, but this has not been studied.*
B) *Thimerosal remains a component of most childhood vaccines, but observational studies have not found a connection with autism.*
C) *Vaccines recommended for children 6 years of age and younger now either contain no thimerosal or contain only trace amounts, because thimerosal was shown to cause autism.*
D) *Vaccines recommended for children 6 years of age and younger now either contain no thimerosal or contain only trace amounts, although observational studies have not found a connection between thimerosal and autism.*

Test questions continue on next page ➞

15. A woman, 70 years of age, who is in generally good health, comes in to discuss some knee pain she has been having. While she is in your office, you take advantage of the opportunity to offer vaccination against seasonal influenza. She tells you that one of her friends is recovering from Guillain-Barré syndrome (GBS), and she recalls hearing something about the flu shot and GBS. What can you tell her?

A) There is a proven risk with some of the current influenza vaccines, but not all.
B) The rumor that incidence of GBS increased with the 1976 swine flu vaccine is untrue.
C) There is a proven risk with the current influenza vaccines, but it is small, about 1 case per 1 million people.
D) There is a theoretical risk with the current influenza vaccines, but even if there is a risk it would probably be small, about 1 case per 1 million people.

16. As of 2024, what is known about HPV and problems following vaccination?

A) The majority of events reported to VAERS have been considered non-serious.
B) Postmarketing reports rule out any connection between vaccination and syncope.
C) The only events reported to VAERS have been non-serious, such as fainting, swelling at the injection site, headache, nausea, or fever.
D) All of the above

17. Research regarding parents' concerns about vaccination suggests that

A) it is unusual for parents to have questions or concerns about vaccines.
B) the majority of parents have some level of uncertainty about vaccinating their children.
C) information from healthcare providers is unlikely to influence decisions about vaccination.
D) information from healthcare providers can have an important impact on parents' decisions to vaccinate.

18. In addition to children who are enrolled in Medicaid, children who are eligible for free vaccines under the Vaccines for Children program include children who

A) are underinsured.
B) have no health insurance coverage.
C) are American Indian or Alaska Native.
D) All of the above

19. You have found that there is room for improvement in pediatric vaccination rates. One of the nurses suggests sending letters to remind both adult patients and the parents of pediatric patients when vaccinations are needed. However, your office manager reminds you that the budget is tight this year. Sending letters would be an extra expense. Based on evidence and current recommendations, what should you do?

A) Either send the letters or institute a system of reminder phone calls.
B) Send letters only for pediatric patients, because reminders work for children but not adults.
C) Do not use letters or phone calls, because reminder systems for patients do not work.
D) Institute a system of reminder phone calls instead of letters, because calls have been proven to have greater effect.

20. Your group practice recently conducted a chart audit and discovered many "missed opportunities" for adult vaccination. You would like to institute a reminder system for yourself and your colleagues, but the others ask if there is any evidence it will work. Based on the evidence, what can you tell them?

A) A review of studies was inconclusive, but a reminder system will do no harm and might help.
B) The office should only use an electronic medical records system, because placing reminders in paper charts has been proven not to work.
C) A review of studies found that physician reminder systems, such as chart notations, stickers, and patient lists, can improve vaccination coverage.
D) Reminder systems for patients work, so even though reminder systems for physicians have not been studied, they can also be expected to increase vaccination rates.

Hyperlipidemias and Atherosclerotic Cardiovascular Disease

Audience
This course is designed for pharmacy and other healthcare p rofessionals who may intervene to limit the effects of hyperlipidemias in their patients, promoting better long-term health and preventing cardiovascular disease.

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

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

1. Discuss the incidence of cardiovascular disorders, expected epidemiologic trends, and relevance to society and healthcare systems.
2. Discuss the relevance of hyperlipidemias in the etiology of atherosclerosis and cardiovascular diseases.
3. Identify risk factors for hyperlipidemias.
4. Describe the exogenous and endogenous pathways of lipid synthesis and metabolism.
5. Describe the various types of lipoproteins.
6. Evaluate lipid profiles and identify the most clinically relevant types of hyperlipidemias.
7. Analyze the importance of lifestyle modification in managing hyperlipidemias.
8. Discuss the targeting of specific steps in lipid synthesis and metabolism related to the mechanism of action of drugs that inhibit cholesterol absorption in the intestine.
9. Describe the therapeutic efficacy and indications of fibrates, statins, and nicotinic acid derivatives.
10. Determine the role of fish oil derivatives and sterols and stanols in the management of hyperlipidemias.
11. Identify patients at risk for coronary heart disease and outline the evidence-based guidelines for the treatment of these patients.

Faculty
A. José Lança, MD, PhD, received his Medical Degree at the University of Coimbra in Coimbra, Portugal, and completed his internship at the University Hospital, Coimbra. He received his PhD in Neurosciences from a joint program between the Faculties of Medicine of the University of Coimbra, Portugal, and the University of Toronto, Toronto, Canada. He was a Gulbenkian Foundation Scholar and was awarded a Young Investigator Award by the American National Association for the Research of Schizophrenia and Depression (NARSAD). (A complete biography can be found online at NetCE.com.)

Faculty Disclosure
Contributing faculty, A. José Lança, MD, PhD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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

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INTRODUCTION AND EPIDEMIOLOGY OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASES

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in developing countries and accounts for 25.7% of all deaths in the United States and 45% of deaths in Europe [1; 2]. According to the World Health Organization (WHO), 17.9 million people die each year from cardiovascular disease, an estimated 32% of all deaths worldwide [3]. It has been estimated that by 2030, ASCVD will account for approximately 23 million annual deaths worldwide, an increase of more than 5 million from current estimates [3].

In developed countries, both the prevalence of ASCVD and the rate of mortality have declined. In the United States, from 2006 to 2016, the number of heart-related deaths declined by 18.6%. The prevalence and mortality rates have decreased as the result of risk factor reduction and advances in diagnosis and medical and surgical treatments [1; 4; 5; 6]. Developing countries, however, are continuing to face an increase in ASCVD, which has been partially attributed to an increased prevalence of hypertension, hyperlipidemia, and diabetes, as well as a 75% increase in tobacco consumption between 1991 and 2001 [7]. Tobacco smoking is among the top three risk factors that account for the most disease burden in China and India [8].

In the United States in 2014–2015, the estimated direct and indirect cost of ASCVD was $351.2 billion [1]. This figure is projected to increase to $1.1 trillion by 2035 [1]. As a comparison, the estimated 2011 annual direct cost of all cancer and benign neoplasms combined is $84 billion, versus $213.8 billion for direct costs of ASCVD [1].

The elevated costs of cardiovascular pathology for individuals, society, and healthcare systems require a novel approach based not only on improved diagnosis and management of disease but primarily on more effective prevention and early intervention. This not only requires a change in general perceptions but also a different approach toward prevention by physicians and other healthcare professionals [9; 10].

The etiology of ASCVD is complex and multifactorial and influenced by a variety of modifiable (e.g., hyperlipidemia, obesity, hypertension, diabetes, smoking, physical inactivity, diet) and non-modifiable (e.g., family history, age, gender) risk factors. Modifiable risk factors play a fundamental role in primary and secondary prevention of ASCVD and account for up to 90% of population-attributable cardiac risk [11; 12].

A high concentration of plasma lipids (i.e., hyperlipidemia), and high concentrations of low-density lipoprotein (LDL) cholesterol in particular, are implicated in the etiology of atherosclerosis and increased incidence of ASCVD such as coro-

nary artery disease, peripheral vascular disease, and ischemic cerebrovascular disease. Hyperlipidemias are also associated with primary hypertension and metabolic syndrome [13; 14].

American Heart Association data from 2015 to 2018 show unfavorable lipid measures of LDL cholesterol >130 mg/dL were present in 27.8% of adults 20 years of age and older, and total blood cholesterol concentrations >240 mg/dL (6.2 mmol/L) were present in 11.5% of adults [234]. Both lipid parameters are associated with excess risk of cardiovascular morbidity and mortality [15].

Hyperlipidemia, and specifically hypertriglyceridemia (150–400 mg/dL or 1.7–4.5 mmol/L), is often present in patients with metabolic syndrome, a disorder characterized by abdominal obesity, hypertension, insulin resistance, low levels of high-density lipoprotein (HDL), and increased risk of ASCVD [13]. Hypertriglyceridemia is also associated with pancreatitis, and severe hypertriglyceridemia has been established as the etiology of up to 7% of pancreatitis. Hypertriglyceridemia-induced pancreatitis rarely occurs unless levels exceed 1,700 mg/dL (20 mmol/L) [16].

Effective lipid management has been shown to slow the progression of atherosclerosis and lower morbidity and mortality of ASCVD [17; 18; 19; 20; 21; 22; 23]. As a result, early diagnosis and appropriate clinical management of hyperlipidemias has become a public health priority in the primary and secondary prevention of ASCVD [24]. Guidelines for the management of hyperlipidemias focus not only on the administration of lipid-lowering drugs but also the implementation of lifestyle changes [24]. Together, these interventions assist with patient adherence and improve clinical outcomes [22; 23]. This approach requires collaboration among all members of the multidisciplinary team of healthcare providers, including physicians, nurses, pharmacists, dietitians, counselors, and physiotherapists [9; 25].

ETIOLOGY OF ATHEROSCLEROSIS

Atherosclerosis results from a chronic inflammatory process that targets medium- and large-sized arteries. This process begins in childhood and progresses slowly with age. However, the condition is rapidly accelerated by a variety of genetic and environmental factors, and hyperlipidemia is a major risk factor in the pathogenesis and progression of atherosclerosis [12; 14; 26; 27].

An elevated concentration of LDL is a major cause of atherosclerosis and increased ASCVD [14; 17; 18; 19; 20; 21; 22]. The causative role of hyperlipidemia has been supported by the finding that decreasing the plasma levels of LDL and triglycerides has a beneficial effect on primary and secondary prevention of ASCVD by reversing, to some extent, the underlying pathology of atherosclerosis [23].

Atherosclerotic vascular disease develops in three progressive stages: fatty streak formation, plaque formation, and plaque disruption [12; 27; 28; 29; 30; 31].

FATTY STREAK FORMATION

Fatty streaks are flat yellow discolorations on the arterial inner (i.e., luminal) surface that neither protrude into the lumen nor disrupt blood flow. The precise mechanisms responsible for the formation of fatty streaks are unclear but endothelial dysfunction is accepted as the primary event in atherogenesis. Physical stressors (e.g., turbulent blood flow at branching points) as well as chemical stressors (e.g., hyperlipidemia, cigarette smoking) alter endothelial cell functions in a complex and interdependent process. This results in:

- Impairment of the role of endothelial cells as a barrier, allowing for the abnormal accumulation of lipids in the sub-endothelial layer and their subsequent transformation (oxidation)
- Release of pro-inflammatory cytokines (e.g., interleukin 1 [IL-1] and tissue necrosis factor-α [TNF-α])
- Release of cell surface adhesion molecules that attract leukocytes (e.g., leukocyte adhesion molecules [LAM], monocyte chemotactic protein 1 [MCP-1], intercellular adhesion molecule 1 [ICAM-1])
- Decreased availability of vasodilator compounds such as nitric oxide and prostacyclin
- Stimulation of prothrombotic effect and platelet aggregation

Together, physical and chemical stressors promote endothelial dysfunction and trigger the initial sub-endothelial accumulation and transformation of oxidized LDL. Initially, oxidized LDL acts as a proinflammatory mediator to attract circulating leukocytes (e.g., monocytes and T-lymphocytes) to the sub-endothelium. Second, dysfunctional endothelial cells and modified smooth muscle cells secrete macrophage-stimulating factors that lead to the expression of scavenger receptors or acetyl-LDL receptors on the surface of macrophages and smooth muscle cells [28]. These scavenger receptors selectively bind to oxidized LDL and promote phagocytosis by macrophages and transformed smooth muscle cells, which become lipid-laden and are known as foam cells. Increased numbers of foam cells and extracellular lipids account for the appearance of fatty streaks [12; 27; 28; 29; 31].

PLAQUE FORMATION

As atherogenesis progresses, arterial fatty streaks increase in size as the result of continuing infiltration by smooth muscle cells, which migrate from the underlying muscular layer and accumulate oxidized LDL, and infiltration by T-lymphocytes, which synthesize and release inflammatory cytokines. These changes increase the number of foam cells and exacerbate local inflammation. In time, extracellular accumulation of

LDL, collagen, elastic fibers, and calcium deposits contribute to the formation of larger and thicker atherosclerotic vascular plaques. Histology shows that atherosclerotic plaques consist of a large lipid core surrounded by a fibrous cap. After decades of development, the plaque grows in size and exhibits features of a chronic inflammatory process within the vessel wall [28]. The arterial wall undergoes a restructuring process that initially grows outward and preserves the lumen diameter. At this stage, the condition is asymptomatic and goes undetected in angiographic studies. As time progresses, larger plaques start to protrude into the lumen and partially disrupt blood flow. Disruption of laminar blood flow also inhibits the expression of superoxide dismutase, a powerful antioxidant, further contributing to oxidation of LDL. This more advanced stage is associated with symptoms of ischemia and may be detected by angiography [12; 27; 28; 29; 31; 32].

PLAQUE DISRUPTION

As noted, the lipid core of atherosclerotic plaque is initially surrounded by a thicker fibrous cap that provides some degree of stability. As plaques grow in size, their lipid cores become increasingly larger with high concentrations of foam cells, extracellular calcification, and accumulation of oxidized LDL. Interestingly, it has been shown that oxidized LDL promotes apoptosis (i.e., programmed cell death) and causes foam cell death, which leads to plaque necrosis, instability, and increased potential for thrombogenesis [33; 34]. At this stage, plaques further protrude into the lumen and disrupt blood flow. Turbulent blood flow increases shear stress in the periphery of the plaque, known as the shoulder region, further increasing risk of instability, plaque disruption, clot formation, and thrombogenesis. These events are often accompanied by symptoms associated with acute ischemia (e.g., angina, myocardial infarction [MI], intermittent claudication, stroke). Lesions at this stage are able to be detected in angiographic studies and ultrasonography [12; 27; 28; 29; 31; 32].

RISK FACTORS FOR HYPERLIPIDEMIA

As discussed, hyperlipidemia has been established as a main risk factor in the development of atherosclerosis and ASCVD. Together with obesity, hypertension, diabetes, smoking, and physical inactivity, hyperlipidemia is a known modifiable risk factor of ASCVD. Additionally, several biomarkers, including C-reactive protein (CRP), hyperhomocysteinemia, and lipoprotein(a), are also considered modifiable risk factors of ASCVD. Modifiable risk factors play a major role in the pathogenesis of ASCVD because they activate the endothelium and stimulate the release of proinflammatory mediators and cell surface adhesion molecules. Because modifiable risk factors account for up to 90% of population-attributable cardiac risk, regulation of these factors has a beneficial effect on the primary and secondary prevention of ASCVD [11; 12].

In addition to modifiable risk factors, the American Heart Association (AHA) and the American College of Cardiology (ACC) have included "risk-enhancing factors" in their 2018 guideline on the management of blood cholesterol (***Table 1***). Projections of future risk derived from primary risk factors and risk-enhancing factors can be used to adjust the intensity of LDL-lowering therapy and enhance clinician-patient risk discussion [24]. When risk is uncertain, a coronary artery calcium score can help facilitate decision-making in adults 40 years of age and older. The identification of familial hypercholesterolemia is a priority in children, adolescents, and young adults. Across all age groups, the emphasis is on reducing lifetime ASCVD risk through a heart-healthy lifestyle [24].

Experimental studies in animals with genetic abnormalities identical to human familial hypercholesterolemia (absence or 50% reduction in LDL receptors in homozygous or heterozygous individuals, respectively) as well as epidemiologic studies of human populations have established that high levels of LDL cholesterol are atherogenic [35; 36; 37]. A number of clinical studies, including the Framingham Heart Study, the Multiple Risk Factor Intervention Trial, and the Lipid Research Clinics, have also reported a direct relationship between elevated concentrations of LDL cholesterol (or total cholesterol) and an increase in cardiovascular morbidity and mortality [1; 17; 18; 19; 20; 21; 23; 25; 38; 39]. Lipid management with a combination of pharmacotherapy and lifestyle changes aimed at the reduction of cholesterol levels effectively slows the progression of atherosclerosis and plays a pivotal role in the primary and secondary prevention of ASCVD [1; 17; 18; 19; 20; 21; 22; 23; 25; 37; 39; 40; 41].

Chronically high levels of CRP, and high sensitivity CRP (hsCRP) in particular, are biomarkers of ASCVD, regardless of whether they play a causal role in atherogenesis or if they are the result of underlying atherosclerosis [12; 27; 42]. The AHA and the Centers for Disease Control and Prevention have issued a joint statement regarding hsCRP values [43]. Concentrations of hsCRP less than 1 mg/L are associated with low risk, and 1–3 mg/L is correlated with moderate risk for ASCVD. Patients with levels greater than 3 mg/L are at high risk for ASCVD [43]. An hsCRP level >10 mg/L has been observed in acute plaque rupture, which may lead to thrombosis [44]. Ongoing clinical studies suggest that lowering the plasma levels of both hsCRP and LDL may be a main goal in the secondary prevention of ASCVD [42].

High homocysteine blood levels (greater than 15 mcmol/L) are associated with increased oxidative stress and secretion of proinflammatory factors. Both mechanisms stimulate smooth cell proliferation and accelerate atherosclerosis [27; 45].

Numerous clinical studies have also revealed that high levels of lipoprotein(a) are associated with significant increases in ASCVD [12; 27; 31; 46; 47; 48]. Lipoprotein(a) is a subtype of LDL that includes apoprotein A (Apo A) in its structure. The role of lipoprotein(a) in atherogenesis relates to a variety of mechanisms including inhibition of fibrinolysis by prevent-

AHA/ACC RISK-ENHANCING FACTORS
• Family history of premature ASCVD (men: age younger than 55 years; women: age younger than 65 years) • Primary hypercholesterolemia (LDL 160–189 mg/dL; non-HDL 190–219 mg/dL[a]) • Metabolic syndrome • Chronic kidney disease (i.e., eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria, not treated with dialysis or kidney transplantation) • Chronic inflammatory conditions (e.g., psoriasis, rheumatoid arthritis, HIV/AIDS) • History of premature menopause (before 40 years of age) and history of pregnancy-associated conditions that increase later ASCVD risk (e.g., pre-eclampsia) • High-risk race/ethnicity (e.g., South Asian ancestry) • Persistently[a] elevated, primary hypertriglyceridemia (≥175 mg/dL) and/or other lipid/biomarkers associated with increased ASCVD risk, including (if measured): – Elevated hsCRP (≥2.0 mg/L) – Elevated Lp(a): a relative indication for its measurement is family history of premature ASCVD. Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a). – Elevated Apo B ≥130 mg/dL: a relative indication for its measurement is triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL >160 mg/dL and constitutes a risk-enhancing factor – ABI <0.9
[a]Optimally, three determinations. ABI = ankle-brachial index; Apo B = Apolipoprotein B; eGFR = estimated glomerular filtration rate; HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome; hsCRP = high-sensitivity C-reactive protein; Lp(a) = lipoprotein(a).
Source: [24] *Table 1*

ing the transformation of plasminogen to plasmin, enhanced capacity to traverse the arterial endothelium, and low affinity for the LDL-receptor mediated clearance from circulation [47]. High lipoprotein(a) concentrations (greater than 30 mg/dL) in patients with an elevated total cholesterol:HDL ratio (greater than 5.5) or other major risk factors indicates the need for a more aggressive therapy to further lower LDL [23; 49].

AN OVERVIEW OF LIPIDS

PHYSIOLOGIC ROLES

Lipids play a crucial role in living organisms as a source of energy and as structural constituents of cell membranes and complex molecules such as steroids and eicosanoids (e.g., prostaglandins, thromboxane A2, leukotrienes) and lipid-soluble vitamins [30; 50; 51]. In brief, the most important lipids are phospholipids, cholesterol, fatty acids, and triglycerides.

Phospholipids are structural components of cell membranes, myelin, lipoproteins, and blood clotting factors. Cholesterol is a structural component of cell membranes and a precursor of other steroids, namely steroid hormones, bile acids, and signaling molecules. Cholesterol is mainly synthesized in the liver but is also absorbed in the intestine from dietary sources and enterohepatic circulation.

Fatty acids are a source of energy. Their general structure is represented as R-COOH, where R represents a hydrocarbon chain. More than 100 fatty acids have been identified, and they differ on length of the hydrocarbon chain and number of carbon-carbon double bonds. Fatty acids without carbon-carbon double bonds are classified as saturated; those with carbon-carbon double bonds are classified unsaturated. Unsaturated fatty acids are further differentiated into monounsaturated or polyunsaturated based on the number of carbon-carbon double-bonds. Saturated fatty acids are waxy solids at room temperature, while unsaturated fatty acids are liquids.

Intracellular free fatty acids are present in trace amounts and esterified with glycerol to form more complex lipids, including triglycerides. Most double bonds in unsaturated fatty acids are in the cis form. Some edible fats, including hydrogenated vegetable products such as oils, margarines, and shortenings, are rich in trans fatty acids. Trans fatty acids (also known as partially hydrogenated fats) have physical properties similar to saturated fats and are solid at room temperature. They are inexpensive to produce, give foods a desirable texture and taste, have a long shelf-life, and can be reused to deep-fry foods. These properties make trans fats particularly attractive to commercial enterprises and fast-food restaurants. However, their increased dietary intake is associated with increased ASCVD. Awareness of this link has led to the concerted effort to decrease or elimi-

nate their availability and dietary intake. Clear information on trans fats, particularly useful for patients and the general population, is readily available from the American Heart Association (***Resources***).

Triglycerides are a combination of three fatty acids attached to a single glycerol molecule. They are the main source of dietary fat and can also be synthesized in the liver from intermediary metabolites of excess carbohydrates. Triglycerides accumulate in adipose tissue and muscle cells and can later be mobilized as non-esterified free fatty acids as a source of energy when dietary sources are not readily available.

Cholesterol and triglycerides have significant roles in the process of atherogenesis. They are virtually insoluble in water, and to facilitate their transport in plasma and lymph, they are packaged in larger spherical macromolecules known as lipoproteins.

ABSORPTION, SYNTHESIS, AND METABOLISM

Circulating lipids have two distinct but interrelated origins and metabolic pathways: the exogenous (i.e., dietary source) and the endogenous pathways (i.e., hepatic synthesis) [52].

Exogenous Pathway

Dietary lipids provide 30% to 40% of calories in Western diets. With the exception of the essential fatty acids (e.g., linoleic, linolenic), most lipids can also be synthesized by humans. Triglycerides, specifically, account for more than 95% of dietary lipid intake. Cholesterol from animal sources and small amounts of plant sterols comprise the majority of dietary lipid intake. Free fatty acids, phospholipids, and fat-soluble vitamins account for the remaining lipids from dietary sources [46; 50; 53].

Dietary fat is digested by enzymes produced in the mouth, stomach, and pancreas. The small intestine is the main site of lipid transformation and absorption. In the small intestine, triglycerides are hydrolyzed by gastric and pancreatic lipases, phospholipids are transformed by phospholipase A2 into lysophospholipids and fatty acids, and cholesterol is hydrolyzed by bile salts and pancreatic hydrolase (also known as cholesterol esterase).

Studies have established that cholesterol absorption in the small intestine is regulated by selective transporters, such as the Niemann-Pick C1 like 1 (NPC1L1). Selective inhibition of NPC1L1 prevents intestinal absorption of dietary cholesterol, a mechanism targeted by ezetimibe, a lipid-lowering drug. In the enterocyte, free cholesterol is esterified to cholesteryl esters by the enzyme acyl-CoA cholesterol acyltransferase isoform 2 (ACAT2) and incorporated into chylomicrons [54].

In a separate pathway, after enzymatic hydrolysis, free fatty acids and monoacylglycerides are transported to the intestinal cells in bile-salt micelles. Micelles deliver the lipid molecules to the enterocyte, and bile salts remain in the lumen, where they are subsequently re-used to form new micelles.

Intracellularly, lipid molecules are re-assembled and packaged in chylomicrons. These are large lipoproteins (75–1,200 nm in diameter) rich in triglycerides and cholesterol but poor in protein content. Chylomicrons are released by exocytosis into the extracellular space, enter the lymphatics, and ultimately reach the bloodstream. Circulating chylomicrons are transformed by lipoprotein lipase, an enzyme expressed in endothelial cells of the capillaries in muscle and adipose tissue, and deliver triglycerides to the muscle (for energy) and adipose tissue (for storage). Chylomicron remnants deliver the cholesterol and the remaining triglycerides to the liver, where cholesterol is used in the synthesis of bile salts and triglycerides and free fatty acids are used in the production of energy by β-oxidation and synthesis of new molecules of cholesterol. The synthesis of cholesterol in hepatocytes is known as the endogenous pathway.

It is relevant to mention that unesterified cholesterol can also be transported back into the intestinal tract by selective transporters, such as the ATP-binding cassette transporters ABCG5 and ABCG8 [55]. A new generation of lipid-lowering drugs that stimulate the ATP-binding cassette transporter is being investigated [56].

Endogenous Pathway

The hepatic pathway is the major source of cholesterol in the body. It is well-established that daily cholesterol synthesis in the liver has a circadian pattern, with lowest levels in the day (30% to 35%) and highest levels at night (65% to 70%). This diurnal rhythm in cholesterol synthesis is regulated by HMG-CoA activity [240]. Selective inhibitors of HMG-CoA reductase, such as statins, effectively prevent the synthesis of cholesterol and are powerful hypolipidemic drugs [31; 57].

Newly formed cholesterol molecules can either be transiently stored in the hepatocytes or further transformed either into bile salts, steroids, or "packaged" in lipoproteins. These lipoproteins, which carry cholesterol and triglycerides from the liver into the circulation, are known as very-low density lipoproteins (VLDL) and have a very high content in triglycerides and cholesterol. VLDLs comprise 15% to 20% of the total blood cholesterol and most of the circulating triglycerides [31; 52].

In the liver, cholesterol is also eliminated by biliary secretion in the form of bile acids. Bile acids, which are highly soluble in water, are released by the hepatocytes into the biliary canaliculi and then transported to the gallbladder, where they are stored in bile and later released into the lumen of the small intestine. Most bile acid molecules (>95%) are not excreted in the feces, but rather are reabsorbed in the ileum, enter the portal circulation, and are then extracted with high first-pass efficiency by hepatocytes. This process of recycling bile acids between liver and intestine is known as enterohepatic circulation. In fact, recycled cholesterol from bile acids is a major source of cholesterol and represents 75% of the total cholesterol that goes through the intestine; dietary cholesterol, even in patients with rich diets, accounts only for up to 25%.

PLASMA LIPOPROTEINS					
Characteristic	**Chylomicrons**	**Very-Low-Density Lipoprotein (VLDL)**	**Intermediate-Density Lipoprotein (IDL)**	**Low-Density Lipoprotein (LDL)**	**High-Density Lipoprotein (HDL)**
Density	<0.95 g/mL	0.95–1.006 g/mL	1.006–1.019 g/mL	1.019–1.063 g/mL	1.063–1.210 g/mL
Diameter	75–1,200 nm	30–80 nm	25–35 nm	18–25 nm	5–12 nm
Protein	2%	10%	18%	25%	33%
Total lipid	98%	90%	82%	75%	67%
Triglycerides	83%	50%	31%	10%	8%
Cholesterol	8%	22%	29%	45%	30%
Phospholipid	7%	18%	22%	20%	29%
Major apoproteins	Apo B-48 Apo C-II Apo E	Apo B-100 Apo C-II Apo E	Apo B-100 Apo C-II	Apo B-100	APO A-I APO A-II Apo C-II Apo E

Source: Compiled by Author *Table 2*

AN OVERVIEW OF LIPOPROTEINS

STRUCTURE AND MOLECULAR COMPONENTS

Triglycerides and cholesterol are non-polar lipids that are virtually insoluble in water. To facilitate their transport in plasma and lymph, they are packaged as lipoproteins. These large spherical macromolecules that transport cholesterol and triglycerides in the plasma vary in size (ranging from 5–1,200 nm in diameter) and density (determined by the ratio of lipid to protein content).

Lipoproteins have a hydrophobic core of non-polar triglycerides and cholesteryl ester (a form of cholesterol linked by an ester bond to a fatty acid) surrounded by a monolayered shell of more water-soluble phospholipids, non-esterified cholesterol, and amphipathic surface proteins known as apoproteins.

Apoproteins (also known as apolipoproteins) are a family of surface proteins that perform three important functions in lipid physiology: stabilize the structure of the lipoprotein shell, activate enzymes in the plasma and endothelial cells, and bind to selective cell receptors [27; 30; 31; 58]. Specific apoproteins regulate the metabolic fate of lipoproteins; their role can be compared to "molecular zip codes" that determine the destination of specific lipoproteins in the body. Each type of lipoprotein contains one or more specific types of apoproteins.

There are four major classes of apoproteins: Apo A, Apo B, Apo C, and Apo E. In terms of clinical relevance, the following lipoproteins are the most important: Apo A-I, Apo A-II, Apo B-100, Apo C, and Apo E [27; 31].

CLASSES OF LIPOPROTEINS AND LIPOPROTEIN PHYSIOLOGY

Lipoproteins are classified by size and density. Because proteins are denser than lipids, the greater the protein content, the greater the density of the lipoprotein. There are five types of lipoproteins: chylomicrons, VLDLs, intermediate-density lipoproteins (IDLs), LDLs, and HDLs (***Table 2***).

Plasma Lipid Profiles

Prior to discussing the properties of the various lipoproteins, it is important to review the most pertinent information related to plasma lipid profiles. In fasting individuals, total cholesterol in plasma is carried primarily in VLDL, LDL, and HDL. Accordingly, total cholesterol is equal to the sum of VLDL, HDL, and LDL.

Clinical laboratories measure total cholesterol, HDL, and triglycerides. Most triglycerides are found in VLDL, which has five times as much triglyceride by weight as cholesterol. Therefore, the amount of cholesterol in VLDL can be calculated as triglycerides (mg/dL) divided by 5 or triglycerides (mmol/dL) divided by 2.2.

For more than 50 years, most clinical laboratories have calculated the value of LDL cholesterol indirectly, according to the Friedewald equation [59; 60]:

LDL (mg/dL) = total cholesterol (mg/dL) – HDL (mg/dL) – [triglycerides (mg/dL) / 5]

Or, if the International System of Units is used, total LDL may be calculated as:

LDL (mmol/dL) = total cholesterol (mmol/dL) – HDL (mmol/dL) – [triglycerides (mmol/dL) / 2.2]

A modified Friedewald equation is also used and has been suggested to have a higher level of accuracy in calculating LDL values [61; 62]. This equation is:

LDL (mg/dL) = [non-HDL cholesterol (mg/dL) x 0.9] – [triglycerides (mg/dL) x 0.1]

It is known that in hypertriglyceridemia, LDL calculated using the Friedewald equation can be unreliable, particularly at levels <70 mg/dL. The increased prevalence of high triglyceride states (e.g., diabetes, obesity) and the use of novel lipid lowering medications (e.g., proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) have provided an impetus for finding improved methods for estimating LDL.

Direct LDL assays are not standardized and can be even less accurate than the Friedewald equation. In one study of seven direct methods for measuring LDL, total assessment errors ranged from 13.3% to 13.5% across assays in healthy individuals and from -26.6% to 31.9% in individuals with known ASCVD or dyslipidemias. The National Cholesterol Education Program has a target total error goal of ≤13%, meaning that all seven direct assays failed standard accuracy goals [63; 64].

Several prior equations have attempted to improve upon the Friedewald equation, but most used the same fixed ratio between triglycerides and VLDL. In a study of more than 1.3 million fasting and nonfasting patients, Martin and colleagues derived and validated a novel equation that replaced the fixed ratio with one of 180 adaptable ratios based on the patient's individual non-HDL and triglyceride values. The overall accuracy of the Martin/Hopkins approach compared with direct measurement was 92% for HDL and 85% for triglycerides. LDL estimation accuracy with the Martin/Hopkins equation was 94%, compared with 77% with the Friedewald method [65]. The 2018 AHA/ACC guideline acknowledges the importance of accurate LDL estimation and recommends measuring LDL either directly or with an alternative method (e.g., the Martin/Hopkins equation) [24; 63].

The ratio of total cholesterol (TC) to HDL (TC:HDL) and the ratio of LDL to HDL (LDL:HDL) are clinically relevant predictors of coronary heart disease (CHD) risk. The lower the ratio value, the better the predicted outcome [66; 67; 68; 69]. The Apo B:Apo A-I lipoprotein ratio has also been used as a predictor for CHD. However, comparative studies have concluded that Apo B:Apo A-I ratio for prediction of CHD "does not provide incremental value for CHD risk prediction over established traditional lipid ratios" [66]. However, the ratio may be useful for evaluating the severity of CHD [70]. A cross-sectional study enrolled 792 patients with angiographically defined CHD following hospital admission. The patients were placed into three groups based on the degree of angiographic atherosclerosis or the number of stenotic coronary branches. Demographic and biochemical data were collected, and lipoprotein ratios were calculated. According to the results, the ratios of LDL:HDL and Apo B:Apo A-I increased with increasing degree of angiographic atherosclerosis, and the ratios of triglyceride:HDL, TC:HDL, LDL:HDL and Apo B:Apo A-I increased with the number of stenotic coronary branches. The ratios of TC:HDL, LDL:HDL, and Apo B:Apo A-I were positively associated with both the degree of atherosclerosis and the number of stenotic vessels, and the ratio of triglyceride:HDL was positively associated with the number of stenotic vessels. The Apo B:Apo A-I ratio was also shown to be a direct mediator between the risk factors of age, BMI, HDL, LDL, and severity of CHD [70].

In adults who are 20 years of age or older and not on lipid-lowering therapy, the ACC/AHA assert measurement of either a fasting or a nonfasting plasma lipid profile is effective in estimating ASCVD risk and documenting baseline LDL. If an individual has ingested an extremely high-fat meal in the preceding eight hours, it may be prudent to assess lipids on another day after counseling the patient to avoid such meals.

(http://www.onlinejacc.org/content/73/24/e285?_ga=2.118995977.141815126.1563751668-1264536891.1558548868. Last accessed July 25, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Chylomicrons

Chylomicrons are large lipoproteins 75–1,200 nm in diameter that are very rich in lipids (98% content), mainly triglycerides (83%) and cholesterol (8%), and have the lowest protein content (2%) of all lipoproteins. Chylomicrons are only synthesized in the intestine and are produced in large amounts during fat ingestion [53]. In normolipidemic individuals they are present in the plasma for 3 to 6 hours after fat ingestion and are absent after 10 to 12 hours fasting [14].

Chylomicrons secreted by intestinal cells are known as "incomplete" chylomicrons because they only express Apo B-48. After entering the lymph and later reaching the bloodstream, chylomicrons interact with circulating HDL, from which they receive Apo C-II and Apo E and then referred to as "complete" chylomicrons. In the capillaries of muscle and adipose tissue, chylomicrons are transformed by the enzyme lipoprotein lipase, a process that requires Apo C-II as a cofactor. As a result of this process, 90% of the triglycerides are hydrolyzed to free fatty acids and glycerol that will be used either as a source of energy in the muscle or stored in the adipose tissue. Individual chylomicrons have a short half-life of 15 to 20 minutes [71]. After interaction with lipoprotein lipase, these cholesterol-rich chylomicron remnants deliver cholesterol and triglycerides to the liver. This process of endocytosis is mediated by a protein, the LDL receptor, expressed on the surface of hepatocytes and requires Apo E and Apo B as cofactors [72].

The concentration of chylomicrons can only be lowered by reducing dietary fat consumption or by drugs that inhibit the intestinal absorption of cholesterol. However, drugs specifically targeting the step of chylomicron secretion have not yet been developed [14]. Although rare, individuals with a genetic deficiency that results in low lipoprotein lipase activity may present with abnormally high concentrations of circulating triglycerides (1,000 –5,000 mg/dL) [31].

Very-Low-Density Lipoproteins

VLDLs are smaller than chylomicrons (80 nm in diameter) and have a very high triglyceride and cholesterol content—five times as much triglycerides by weight as cholesterol. As noted, VLDL makes up 15% to 20% of the total blood cholesterol and most of the circulating triglycerides [73].

In the muscle and adipose tissue capillaries, lipoprotein lipase interacts with circulating VLDL, from which it removes triglycerides in a process that requires Apo C-II as a cofactor, as described for chylomicrons. VLDL also expresses Apo E and Apo B-100. Apo B-100 plays a fundamental role in the regulation of circulating cholesterol.

From a metabolic viewpoint, both chylomicrons and VLDL deliver triglycerides to muscle and adipose tissue [30]. However, whereas chylomicrons are an integral part of the exogenous pathway and carry dietary lipids, VLDL transport triglycerides and cholesterol synthesized in the liver as a part of the endogenous pathway. From a clinical perspective, it is particularly relevant to point out that the hepatic synthesis of VLDL is increased when the concentration of free fatty acids in the liver is increased (e.g., in high-fat diets) as well as when adipose tissue releases high amounts of free fatty acids in the circulation (e.g., as a result of obesity or diabetes) [46]. Genetic deficiencies that result in either total (abetalipoproteinemia) or partial liver failure to produce Apo B-100 (familial hypobetalipoproteinemia) inhibit the release of VLDL by hepatocytes and result in fatty liver [74].

Intermediate-Density Lipoproteins

IDLs, also known as VLDL remnants, are created when VLDL is depleted in triglycerides as a result of the hydrolysis by the enzyme lipoprotein lipase. IDLs have a short half-life (less than 30 minutes) and undergo liver absorption by selective uptake mainly by binding to the LDL receptor, with Apo B-100 and Apo E as required cofactors. Genetic variants of Apo E are responsible for low binding to the LDL receptor, which results in high concentrations of circulating VLDL and IDL, a condition clinically known as type III hyperlipoproteinemia [14; 75].

Low-Density Lipoproteins

LDLs play a central role in atherogenesis and are often called "bad cholesterol." The discovery of the LDL receptor by Goldstein and Brown and their work elucidating its role in cholesterol homeostasis is one of the most important advances in cardiovascular research. Their studies have been a major contribution to the understanding of the mechanisms underlying hyperlipidemias [72]. The proatherogenic role of LDL on the release of pro-inflammatory cytokines (e.g., IL-1, TNF-α) and adhesion molecules (e.g., LAM, ICAM-1) is well established.

LDLs are the product of VLDL and IDL metabolism by lipoprotein lipase. LDL is the most cholesterol-rich of all lipoproteins, and even in healthy individuals, LDLs carry two-thirds of the circulating cholesterol [14]. LDL has a half-life of 1.5 to 2 days, which accounts for a plasma concentration higher than VLDL and IDL [14; 46; 53; 57].

There are several subtypes, also known as subfractions, of LDL, and it has been proposed that smaller, denser LDL particles are more atherogenic than larger and less dense LDL. However, research suggests that the use of clinically available LDL subfractions to estimate the risk of ASCVD is premature [76; 77; 78].

Plasma clearance of LDL is primarily mediated by the LDL receptor expressed on the cell surface. Although LDL receptors are expressed in various cell types, approximately 75% of all LDL receptors are expressed in hepatocytes [79]. The uptake of LDL in hepatocytes is mediated by the interaction between the LDL receptor and Apo B-100 (the only apoprotein expressed in LDL), which acts as a ligand at the LDL receptor. This selective and highly effective mechanism accounts for the extraction of approximately 75% of all LDL from plasma [80]. Hepatic LDL receptors are downregulated by the high delivery of cholesterol by chylomicrons or dietary saturated fat and upregulated by decreased cholesterol and saturated fat intake [46; 81].

The crucial role of LDL in atherogenesis results from it being oxidized in the arterial subendothelium. Oxidized LDL has a high affinity for the scavenger receptor expressed in macrophages undergoing endocytosis, which leads to intracellular accumulation and the transformation of lipid-rich macrophages into foam cells.

Genetic mutations of either the LDL receptor or Apo B-100 alter the effectiveness of the binding and increase the plasma concentration of LDL. Familial hypercholesterolemia and familial defective Apo B-100 are examples of clinical conditions that result from these genetic mutations [82; 83]. Homozygotes for familial hypercholesterolemia inherit two mutant LDL receptor genes and present with a 6- to 10-fold elevation in plasma LDL from birth. These patients suffer from advanced CHD starting in early childhood [72; 84].

The expression of LDL receptors in the liver is also regulated by the intracellular enzyme HMG-CoA reductase. Inhibition of HMG-CoA reductase, for example by the administration of statins, not only results in direct inhibition of the intracellular synthesis of cholesterol but indirectly increases the expression of LDL receptors and therefore promotes the LDL-receptor-mediated removal of circulating cholesterol.

The LDL receptor is also relevant from a clinical perspective because both thyroid hormones and estrogens stimulate its expression in the liver [80; 85]. Consequently, deficiencies of these hormones decrease the availability of LDL receptors and result in increased concentrations of circulating LDL and increased risk of ASCVD [14; 80].

The subtype of lipoprotein(a) is associated with increased risk for ASCVD [12; 27; 31; 46; 47]. Lipoprotein(a) has a similar lipid composition to more typical LDL but has a higher protein content [86]. The atherogenic role of lipoprotein(a) relates to its unique molecular properties and results in the inhibition of fibrinolysis, enhanced capacity to traverse the arterial endothelium, and low affinity for the LDL-receptor-mediated clearance from circulation [47]. Lipoprotein(a) also exhibits platelet activating and pro-inflammatory properties that further contribute to atherogenesis [87]. Patients with high levels of lipoprotein(a) (greater than 30 mg/dL) and an elevated total cholesterol:HDL ratio (>5.5) or other major risk factors require a more aggressive therapy to lower LDL [23; 49]. Lowering circulating LDL remains the primary goal in the treatment and prevention of atherosclerosis and ASCVD [15; 22; 24].

High-Density Lipoproteins

HDLs are the smallest (5–12 nm in diameter) but the densest lipoproteins (33% protein content). HDL removes cholesterol from the periphery and transports it to the liver [53]. HDLs are a heterogeneous population classified based on size, density, and apoprotein content. The two most important subclasses of HDL express either Apo A-I alone or both Apo A-I and A-II, but the clinical relevance of the various subtypes is unknown [88].

HDL concentration in the plasma is inversely related to the risk of ASCVD, and for this reason HDL is also known as "good cholesterol." The role played by HDL in the transport of cholesterol from the periphery to the liver, known as reverse cholesterol transport, and subsequent excretion in bile is a very well-understood mechanism through which HDL protects against atherosclerosis [88; 89].

Two main factors are involved in cholesterol removal from the periphery. First, a cell membrane protein (ABCA1) promotes the efflux of cholesterol from cell membranes; second, ABCA1 interacts with Apo A-I from HDL and captures cholesterol. Cholesterol, in the form of cholesteryl esters, is subsequently transferred to LDL, which will carry it to the liver. In the liver, hepatic extraction requires binding to the LDL receptor. Genetic mutations that cause loss of function of ABCA1 result in extremely low levels of HDL and cholesterol accumulation in the liver, spleen, tonsils, and central and peripheral nervous systems. This results in early-life coronary and peripheral artery disease, a condition known as Tangier disease or familial alpha-lipoprotein deficiency [90; 91].

In vitro and in vivo studies have revealed that HDL has anti-inflammatory and antioxidant properties and inhibits atherogenesis. It has been suggested that high levels of HDL have a protective effect on the development of atherosclerosis and ASCVD [88; 92].

However, authors of a systematic review of clinical studies concluded that "simply increasing the amount of circulating HDL does not necessarily confer cardiovascular benefits" and that reduction of LDL should remain "the primary goal for lipid-modifying interventions" [93]. Other researchers concluded that raising endogenous HDL levels in humans to reduce the development of atherosclerosis "has yet to be established conclusively" [88]. Together, these studies further support the recommendation that lowering LDL should remain the target goal for patients with hyperlipidemia and/or at risk for ASCVD-related conditions [22; 24].

CLASSIFICATION OF HYPERLIPIDEMIAS

Hyperlipidemias, also known as dyslipidemias, are elevations of LDL cholesterol either alone or in conjunction with triglycerides. As noted, they may also be associated with low HDL.

In 2013, the National Heart, Lung, and Blood Institute (NHLBI) discontinued its publication of clinical practice guidelines, instead choosing to provide its systemic evidence reviews to professional organizations, who then publish guidelines based on these and other findings [94]. This change affected five cardiovascular disease-related documents that were in the process of being crafted, including those addressing cholesterol, blood pressure, risk assessment, lifestyle interventions, and obesity. The AHA and the ACC published guidelines intended to update the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) recommendations in 2013, but these guidelines focused primarily on optimal statin use and did not address specific risk factors or lifestyle changes [95].

In the 2013 ACC/AHA update to the NCEP-ATP III, one major change in the treatment recommendations was the removal of specific LDL and non-HDL-cholesterol target values. The NCEP-ATP III guidelines indicated that the target goal for LDL should be <100 mg/dL; however, the Expert Panel determined that there was not sufficient evidence to support treatment to a specific target goal [96; 97]. The 2018 AHA/ACC update to the 2013 guideline includes a limited restoration of LDL treatment targets, particularly in higher-risk groups, based on the results of U.S. population studies and randomized controlled trials confirming the general principle that for LDL, "lower is better" [24]. For the purposes of this course, the 2018 AHA/ACC guideline recommendations will be discussed.

Hyperlipidemias are classified by etiology as primary or secondary, or by phenotype according to identification of lipoprotein patterns, as with Fredrickson phenotypic classification (***Table 3***). In practice, a combination of both classifications is used, as the patient's condition is first identified based on clinical evidence and lipid profile, providing the data required for classification based on etiology [31; 46; 67; 79; 98].

Advances in genetics, genomics, and proteomics have contributed to a better understanding of the pathophysiology of numerous diseases and to the development of new and selective therapies. However, their contribution to the study of primary hyperlipidemias is still limited [99]. While gene therapy is being developed to treat some patients with known genetic abnormalities, the genetic profile and molecular basis

LIPOPROTEIN PATTERNS OF HYPERLIPIDEMIAS (FREDRICKSON PHENOTYPES)		
Phenotype	**Elevated Lipoproteins**	**Elevated Lipids**
I	Chylomicrons	Triglycerides
IIa	LDL	Cholesterol
IIb	LDL and VLDL	Triglycerides and cholesterol
III	VLDL and chylomicron remnants	Triglycerides and cholesterol
IV	VLDL	Triglycerides
V	Chylomicrons and VLDL	Triglycerides and cholesterol
Source: [46; 98]		*Table 3*

of primary hypertriglyceridemia has been determined in only 5% to 10% of cases, and the percentage is even lower for secondary hyperlipidemia [100; 101; 102].

PRIMARY HYPERLIPIDEMIAS

Primary hyperlipidemias result from single or multiple genetic mutations that target any of the molecules that participate in the endogenous and exogenous lipid pathways. These mutations result in increased plasma concentrations of cholesterol (pure or isolated hypercholesterolemia), triglycerides (pure or isolated hypertriglyceridemia), or both (mixed or combined hyperlipidemia) and are the result of either increased synthesis or decreased clearance. HDL concentrations may be lower than normal, either from decreased synthesis or increased clearance.

At the early stages, primary hyperlipidemias are asymptomatic. However, as the disease progresses, a constellation of signs and symptoms develop, such as eruptive xanthomas (located on the trunk, back, buttocks, elbows, knees, hands, and feet), severe hypertriglyceridemia (greater than 2,000 mg/dL), lipemic plasma (i.e., plasma develops a creamy supernatant when incubated overnight), and lipemia retinalis (i.e., creamy white-colored blood vessels in the fundus) often associated with premature CHD or peripheral vascular disease [46; 100; 103].

Familial hypercholesterolemia and familial defective Apo B-100 are examples of clinical conditions that result from LDL receptor and Apo B-100 deficiencies, respectively [82; 83; 104]. Other genetic mutations cause familial hypertriglyceridemia, familial combined hyperlipidemia, familial chylomicronemia, and familial dysbetalipoproteinemia [31; 46; 100; 105; 106].

Polygenic hypercholesterolemia, also known as nonfamilial hypercholesterolemia, is the most common form of hyperlipidemia, with a prevalence of more than 25% in the American population [106]. Polygenic hypercholesterolemia is a typical example of the combination of multiple genetic deficiencies that result in decreased activity of the LDL receptor and reduction of LDL clearance. This underlying genetic susceptibility, not yet completely understood, becomes apparent with dietary intake of saturated fats, obesity, and sedentary lifestyle. Twenty percent of polygenic hypercholesterolemia patients have a family history of CHD. Patients present with mild-to-high increases in total cholesterol (250–350 mg/dL or 6.5–9.0 mmol/L) and LDL (130–250 mg/dL or 3.33–6.45 mmol/L). A combination of lifestyle changes (e.g., reduction in saturated fat) and lipid-lowering drugs (e.g., statins, bile acid sequestrants, ezetimibe, niacin) effectively control the condition [31; 107].

Familial hypercholesterolemia is an autosomal dominant disease responsible for defective LDL receptors that results in either reduction in receptor synthesis or inability of the receptor to bind and/or efficiently remove LDL. The heterozygous form (caused by a single abnormal copy of the gene) has a prevalence of 1 per every 500 in the United States, and the homozygous form (from two abnormal copies) occurs in 1 of every 1 million Americans [107; 108]. Patients typically present with tendon xanthomas, premature MI (5% by 30 years of age and 50% by 50 years of age in untreated heterozygotes), elevated total cholesterol (275–500 mg/dL in heterozygotes and 700–1,200 mg/dL in homozygotes), and elevated triglycerides (250–500 mg/dL in heterozygotes and >500 mg/dL in homozygotes) [107; 108]. Familial hypercholesterolemia heterozygotes respond to lifestyle changes and drug therapy that combines statins with other drugs that upregulate the LDL receptors, such as bile acid sequestrants, ezetimibe, or niacin. Due to the high risk of CHD and MI in homozygous patients, the clinical management requires early treatment in medical centers specialized in lipid treatment and often requires LDL apheresis (i.e., extracorporeal removal of LDL) and liver transplantation [30; 31; 46; 107; 108]. Three drugs have been approved by the U.S. Food and Drug Administration (FDA) for homozygous familial hypercholesterolemia since 2012, a microsomal triglyceride transfer protein inhibitor (lomitapide), an antisense oligonucleotide inhibitor (mipomersen), and an adenosine triphosphate-citrate lyase inhibitor (bempedoic acid). A box warning for risk of hepatotoxicity was added to mipomersen in 2016. Lomitapide and mipomersen inhibit the synthesis of Apo B–100, while bempedoic acid inhibits renal tubular organic anion transporter 2 [109; 110; 233]. Familial hypertriglyceridemia is a common autosomal dominant disease characterized by high triglycerides (200–500 mg/dL or 2.3–5.7 mmol/L) and normal LDL. Lipid-lowering drugs (e.g., fibrates, niacin, statins) combined with diet and weight loss are the most appropriate therapy [30].

SECONDARY HYPERLIPIDEMIAS

Secondary hyperlipidemias are associated with primary underlying conditions such as obesity (increased triglycerides and decreased HDL), diabetes (increased triglycerides and increased total cholesterol), alcohol abuse (increased triglycerides and increased HDL), chronic renal insufficiency (increased total cholesterol and increased triglycerides), and hypothyroidism (increased total cholesterol). It has been postulated that these events expose an underlying genetic or metabolic deficiency that increases the individual's susceptibility to develop hyperlipidemia [31; 100].

Along with polygenic hypercholesterolemia, atherogenic dyslipidemia is one of the most common forms of hyperlipidemias. Atherogenic dyslipidemia is found in approximately 25% of patients with dyslipidemias and is usually diagnosed in patients with metabolic syndrome. In atherogenic dyslipidemia patients there is increased mobilization of triglycerides and cholesterol from adipose tissue to the circulation. This results in increased concentrations of triglycerides and VLDL rich in Apo C-III. Apo C-III inhibits lipoprotein lipase and prevents extraction of triglycerides from VLDL. Moderate-to-high increases in triglycerides (150–500 mg/L or 1.69–5.65 mmol/dL) result from high fat intake and mobilization from adipose tissue and VLDL secretion by the liver. These patients are treated with lifestyle changes aimed at weight reduction and increasing physical activity (which stimulates lipoprotein lipase activity). Statins (to lower VLDL) and fibrates (to lower triglycerides) are the most appropriate drugs to complement lifestyle changes [31; 111]. Studies support the use of antioxidants as well as newer fibrates in the treatment of atherogenic dyslipidemia based on their agonism at the peroxisome proliferator-activated receptor α (PPAR-α) [112; 113].

Secondary hyperlipidemias can also be associated with a number of drug-induced conditions such as estrogen therapy (increased triglycerides and increased total cholesterol), atypical antipsychotics (increased triglycerides), corticosteroids (increased total cholesterol), selective α-blockers without intrinsic sympathetic activity or α-antagonism (increased total cholesterol and decreased HDL), and thiazides (modest increase in total cholesterol and LDL) [67; 114].

In summary, secondary hyperlipidemias with elevated triglycerides are the primary lipid abnormality in patients with obesity, diabetes, alcohol abuse, hormone replacement therapy, and atypical antipsychotic therapy. Secondary hyperlipidemias with elevated cholesterol are the main dyslipidemia in patients with chronic renal failure, hypothyroidism, and typical β-blocker use (e.g., propranolol, atenolol).

From a clinical perspective, identifying the lipid profile, classifying the hyperlipidemia, and managing comorbidity are each necessary in order for patients to achieve lower cholesterol and triglyceride levels required to reduce ASCVD risk [22; 25; 46; 100; 105].

APPROACHES TO CLINICAL MANAGEMENT OF HYPERLIPIDEMIAS

Management of existing hyperlipidemia is a cornerstone in the prevention and management of ASCVD. In large randomized controlled trials, LDL lowering has been consistently shown to reduce the risk of ASCVD. However, in clinical practice, absolute responses in LDL levels to statin therapy depend on baseline LDL levels and the intensity of lipid-lowering therapy. Furthermore, it is important to bear in mind that as cardiovascular risk increases, so does the absolute benefit of therapeutic interventions proven to lower LDL cholesterol levels; both the absolute risk and the magnitude of LDL cholesterol level reduction achieved are important [235]. A given dose of statins produces a similar percentage reduction in LDL levels across a broad range of baseline levels; therefore, percentage reduction is a more reliable indicator of statin efficacy. The 2018 AHA/ACC guideline uses percentage reduction to estimate the efficacy of statin therapy, with the primary goal being a ≥ 50% reduction in LDL levels [24].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The U.S. Preventive Services Task Force (USPSTF) recommends that adults without a history of cardiovascular disease (CVD) use a low- to moderate-dose statin for the prevention of cardiovascular events and mortality when all of the following criteria are met:

- They are 40 to 75 years of age.
- They have one or more CVD risk factors.
- They have a calculated 10-year risk of a cardiovascular event of 10% or greater.

Identification of dyslipidemia and calculation of 10-year CVD event risk requires universal lipids screening in adults 40 to 75 years of age.

(https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/statin-use-in-adults-preventive-medication. Last accessed July 25, 2022.)

Strength of Recommendation/Level of Evidence: B (There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.)

Hypertriglyceridemia is associated with an increased risk of ASCVD events and acute pancreatitis, and lowering triglyceride levels in high-risk patients (e.g., those with ASCVD or diabetes) is associated with decreased cardiovascular morbidity and mortality. The management of mixed dyslipidemia remains controversial, so treatment should focus primarily on lowering LDL levels [105].

AHA/ACC RECOMMENDATIONS FOR ASSESSMENT OF BASELINE LEVELS OF LDL AND NON-HDL
In adults 20 years of age or older not on lipid-lowering therapy, measurement of either a fasting or a nonfasting plasma[a] lipid profile is effective in estimating ASCVD risk and documenting baseline LDL (Class I, based onmoderate-quality evidence).
In adults 20 years of age or older in whom an initial nonfasting lipid profile reveals a triglyceride level of ≥400 mg dL (≥4.5 mmol/L), perform a repeat lipid profile in the fasting state for assessment of fasting triglyceride levels and baseline LDL (Class I, based on moderate-quality evidence).
For patients with an LDL level <70 mg/dL (<1.8 mmol/L), measurement of direct LDL or modified LDL estimate is reasonable to improve accuracy over the Friedewald formula (Class IIa, based on limited data).
In adults 20 years of age or older without a personal history of ASCVD but with a family history of premature ASCVD or genetic hyperlipidemia, measurement of a fasting plasma lipid profile is reasonable as part of an initial evaluation to aid in the understanding and identification of familial lipid disorders (Class IIa, based on limited data).
[a]Both fasting and nonfasting total cholesterol and HDL levels appear to have similar prognostic value and associations with ASCVD outcomes. Therefore, nonfasting samples can be used for risk assessment in primary prevention and for assessment of baseline LDL levels prior to initiation of a statin. If more precision is necessary, fasting lipids can be measured, but a nonfasting sample is reasonable for most situations.
Source: [24] *Table 4*

Baseline levels are used to estimate risk of ASCVD, guide treatment decisions, and accurately evaluate response to therapy. It is important to note that baseline cholesterol levels may vary by geography and among ethnic minority populations. For example, cholesterol values are about 20% higher in the Western population than in the Asian population [67]. The 2018 AHA/ACC guideline provides recommendations for the accurate measurement of baseline LDL levels (***Table 4***) [24; 63].

LIFESTYLE MODIFICATION

Management of hyperlipidemia is but one component of a general strategy for reducing the risk of ASCVD. It is important that healthcare professionals have a good understanding of other measures required for effective risk reduction, including lifestyle changes that may facilitate lipid management before there is need of pharmacotherapy. The 2019 AHA/ACC Guideline on the Primary Prevention of Cardiovascular Disease presents recommendations related to lifestyle modification (e.g., diet and physical activity), patient comorbidities (e.g., obesity, diabetes, hypertension), and patient-centered approaches (e.g., team-based care, shared decision-making, assessment of social determinants of health) to management [236]. The recommendations for management of hyperlipidemia in the AHA/ACC 2018 Cholesterol Clinical Practice Guidelines have been included in the 2019 AHA/ACC guideline.

The ACC/AHA recommend a diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish decrease ASCVD risk factors. (http://www.onlinejacc.org/content/73/24/e285?_ga=2.118995977.141815126.1563751668-1264536891.1558548868. Last accessed July 25, 2022.)

Level of Evidence: I (Strong)

Modifiable lifestyle factors for cardiovascular disease risk reduction include diet, weight reduction, physical activity (exercise), and smoking cessation [24; 236]. The 2018 AHA/ACC guideline on management of blood cholesterol and 2019 guideline on primary prevention of cardiovascular disease concur on the recommendations for good nutrition, diet, and exercise [24; 236]. All adults should consume a healthy diet that [236]:

- Emphasizes the intake of fruits, vegetables, nuts, and whole grains
- Includes low-fat dairy products, poultry, fish, legumes, and nontropical vegetable oils
- Limits the intake of sweets, sugar-sweetened beverages, refined carbohydrates, red meat, and processed meats
- Replaces saturated fat (no more than 5% to 6% of calories from saturated fat) with dietary monounsaturated and polyunsaturated fats
- Avoids the intake of trans fat

It is important to adapt the dietary pattern to the patient's calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions, including diabetes. For adults with obesity, counseling and caloric restriction are recommended for achieving and maintaining weight reduction [236]. A successful dietary approach to lipid lowering requires instruction by a dietitian or other knowledgeable healthcare professional.

Instructions to patients should not be presented as a list of "foods to avoid" but rather should provide dietary alternatives and teach the patients how to make appropriate dietary choices and control portions. A balanced diet, particularly in the modality known as the Mediterranean diet, is associated with a significant reduction in cardiovascular events and mortality [116; 117; 118]. The Mediterranean diet is characterized by meals predominately consisting of vegetables/fruits, lean protein, and healthy fats (e.g., olive oil) and the moderate consumption of wine. Plans such as those offered by the USDA's Dietary Guidelines for Americans, the AHA Diet and Lifestyle Recommendations, and the DASH Eating Plan can also help the patient achieve recommended lifestyle changes [119; 120; 121].

Physical activity stimulates the activity of lipoprotein lipase in adults as well as in children, lowers triglycerides and VLDL, and promotes cardiovascular fitness and weight loss [31; 122]. Adults should engage in 150 minutes per week of accumulated moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity to reduce ASCVD risk [236]. An example of moderate exercise is brisk walking; examples of vigorous exercise are swimming, biking, and playing tennis. Combining moderate and vigorous physical activity allows for a proportionate reduction in time allotted to exercise each week.

Although dietary changes should always be included in the treatment of hyperlipidemias, the length of time given to lifestyle changes prior to initiation of pharmacotherapy remains controversial. In patients with low cardiovascular risk, it has been proposed that the efficacy of dietary and other lifestyle changes can be assessed in two to three visits over a two- to three-month period. Drug therapy is recommended only in select patients with moderately-high LDL (≥160 mg/dL) or patients with very-high LDL (190 mg/dL). High-intensity or maximal statin therapy plus ezetimibe and/or a PCKS9 inhibitor is recommended for the patient at very-high risk (i.e., history of multiple major ASCVD events) [24].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

Because patient education is such a vital aspect of encouraging lifestyle changes in patients with elevated lipid levels, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. 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.

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/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.

LIPID-LOWERING MEDICATIONS

Prior to discussing specific therapeutic indications of lipid-lowering drugs in the treatment of hyperlipidemias, it is timely to summarize their relevant mechanisms of action and therapeutic properties. The subsequent sections provide updated information regarding the pharmacologic properties and clinical profile of lipid-lowering drugs and uses the pharmacologic resources and therapeutic guidelines recommended in North America, as well as current drug information [25; 30; 31; 46; 57; 105; 100; 123; 124; 125; 126; 127; 128].

DRUGS THAT INHIBIT CHOLESTEROL ABSORPTION IN THE INTESTINE

Bile Acid-Binding Resins

Mechanism of Action and Clinical Pharmacology

Bile acid-binding resins, also known as bile acid sequestrants, are cationic polymers that bind to the negatively charged bile acids in the lumen of the intestine. The bile-acid complex cannot be absorbed by the intestinal mucosa and is subsequently eliminated in the feces [129]. Bile acids are the source of 75% of cholesterol in the intestine, and inhibition of their reabsorption effectively disrupts chylomicron formation and decreases the availability of cholesterol and triglycerides in the liver.

Under certain circumstances, the ACC/AHA assert that nonstatin medications (i.e., ezetimibe, bile acid sequestrants, and PCSK9 inhibitors) may be useful in combination with statin therapy.

(http://www.onlinejacc.org/content/73/24/e285?_ga=2.118995977.141815126.1563751668-1264536891.1558548868. Last accessed July 25, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

These events upregulate 7α-hydroxylase, also known as cytochrome P450 7A1 (CYP7A1), the enzyme responsible for the synthesis of bile acid in the liver. This increases the conversion of cholesterol to bile acid synthesis in hepatocytes. Consequently, the intracellular recruitment of cholesterol to bile acid synthesis both depletes its intracellular storage and upregulates the expression of LDL receptors to remove

circulating cholesterol. Ultimately, the therapeutic benefit of these drugs is to lower circulating LDL by 10% to 24% [30].

The LDL-lowering benefit of bile acid-binding resins is offset in the long term by the upregulation of cholesterol and triglyceride synthesis and a possible increase in VLDL synthesis. Accordingly, these drugs should be used cautiously in patients with hypertriglyceridemia.

Bile acid-binding resins lower the incidence of coronary events in middle-aged men by about 20%, with no significant effect on total mortality [67]. Overall, bile acid-binding resins have a solid safety record, have been shown to lower LDL by 10% to 24%, and help reduce the risk of CHD [30; 31; 130; 131]. Colesevelam, the newest drug in this class, lowers glycated hemoglobin and fasting plasma glucose and is approved as add-on therapy for glycemic control in select patients with type 2 diabetes [109; 132].

Adverse Effects

Bile acid-binding resins have very low potential to cause systemic adverse effects because they are not absorbed systemically. However, some patients may report gastrointestinal symptoms, including constipation (10%), dyspepsia, and bloating (1% to 8%) [109; 133].

Drug Interactions

The bile acid-binding resins cholestyramine, colestipol, and to a lesser extent colesevelam inhibit intestinal absorption of a variety of lipophilic drugs. This includes fat-soluble vitamins (A, D, E, and K), corticosteroids, estrogens, progestins, thyroid and thyroxine preparations, and negatively charged (i.e., acidic) compounds such as warfarin, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, valproic acid, folic acid, furosemide and thiazide diuretics, digitalis glycosides, tetracyclines, propranolol, and the oral antidiabetic drugs glipizide, troglitazone, and glyburide. These drug interactions increase intestinal elimination of the drug-resin complexes, resulting in decreased absorption, drug bioavailability, and therapeutic efficacy.

Cholesterol Absorption Inhibitors

Mechanism of Action and Clinical Pharmacology

Cholesterol absorption inhibitors block the intestinal absorption of cholesterol of dietary and biliary origin as well as plant sterols. Plant sterols (also known as phytosterols) and ezetimibe block the absorption of cholesterol in the intestine through two different mechanisms of action. Phytosterols are more hydrophobic than cholesterol and displace the latter from micelles, promoting its intestinal elimination. The absorption of sterols and cholesterol across cells of the intestinal lumen requires the participation of the molecular transporter NPC1L1. Sterol binding to the NPC1L1 transporter further inhibits cholesterol absorption. Sterols are available from plant sources, dietary fiber supplements, and plant sterol-enriched margarines. If absorbed in the intestine, sterols' action against cholesterol is compromised.

Ezetimibe selectively targets and inhibits the transporter NPC1L1, preventing the uptake of cholesterol and phytosterol across the intestinal lumen. Inhibition of cholesterol absorption increases the expression of hepatic LDL receptors and enhances clearance of LDL from the circulation. Ezetimibe is indicated as adjunctive therapy to diet for the reduction of total cholesterol, LDL, and Apo B in patients with primary (heterozygous familial and nonfamilial) hyperlipidemia [109; 133]. It lowers LDL by 15% to 20% and causes minimal increases in HDL, but its beneficial effect on prevention of CHD remains unclear. This agent is synergistic with statins and, if taken in conjunction, can lower LDL by up to 25% in addition to the results obtained by statins alone [109; 134]. Ezetimibe is available in a combination formulation with the statin simvastatin under the brand name Vytorin. A second combination formulation combining ezetimibe with the statin atorvastatin, brand name Liptruzet, received FDA approval in 2013. However, Liptruzet was recalled in 2014 for packaging issues and discontinued in 2016 [109; 133; 135; 136].

Ezetimibe reduces cholesterol absorption by approximately 50%. However, quite unlike the bile acid-binding resins, it does not prevent the absorption of triglycerides or fat-soluble vitamins, and the effects of ezetimibe in the prevention of CHD have not yet been clearly established [30; 46; 67; 137; 138].

Adverse Effects

Upper respiratory tract infection (4%), sinusitis (3%), diarrhea (4%), arthralgia (3%), and pain in an extremity (4%) are the most commonly reported adverse events associated with these medications [109].

Drug Interactions

Ezetimibe interacts with cyclosporine, cholestyramine, and fibrates. The combination of ezetimibe with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases, as well as in pregnant and nursing women [109; 133].

FIBRATES

Mechanism of Action and Clinical Pharmacology

Fibrates, also known as fibric acid derivatives, are agonists at the PPAR-α. These nuclear receptors are expressed primarily in hepatocytes and muscle cells, and their stimulation by fibrates results in activation of specific genes and subsequent changes in lipid metabolism. The lipid-lowering properties of fibrates result from multiple mechanisms of action, namely activation of lipoprotein lipase, which lowers triglycerides and VLDL; inhibition of Apo C-III synthesis in the liver, preventing the inhibitory action of Apo C-III on lipoprotein lipase activity; and stimulation of Apo A-I and Apo A-II expression, which increases HDL levels [139].

The removal of triglycerides from chylomicrons alters the size and composition of LDL from small, dense particles (which are thought to be more atherogenic due to their susceptibility to oxidation) to large, buoyant, and less atherogenic particles

that have a greater affinity for LDL receptors and are rapidly cleared from the plasma. The fibrates fenofibrate, gemfibrozil, and bezafibrate decrease triglyceride levels by 20% to 50%, increase HDL 10% to 20%, and lower LDL by about 5% to 15%, although the latter result is quite variable [109].

Fibrates are indicated in the treatment of hypertriglyceridemias and dysbetalipoproteinemia and in individuals with moderately elevated triglyceride levels (150 – 400 mg/dL or 1.7 – 4.5 mmol/L), a sign often associated with metabolic syndrome. Fibrates are also indicated in the prevention of pancreatitis in patients with severely high triglyceride levels (greater than 1,000 mg/dL or 11.3 mmol/L) [109].

Fibrates are one of the most prescribed lipid-lowering drugs, second only to statins, and it is clinically relevant that they have been shown to reduce fatal and non-fatal ASCVD by about 20%, although their effect on LDL, as mentioned previously, is limited and variable.

Adverse Effects

Fibrates are usually well tolerated. Gastrointestinal side effects such as diarrhea, nausea, dyspepsia, and abdominal pain, are reported by 5% of patients. Even less common adverse effects include skin rash, myalgias, headache, and impotence [109].

Drug Interactions

Myositis occurs in up to 5% of patients taking a fibrate who are also being treated with statins. When combined with statins, fenofibrate is the preferred drug because it has less risk of rhabdomyolysis compared with gemfibrozil [140].

Fibrates potentiate the effects of oral anticoagulants (e.g., warfarin), as they compete for their binding sites to albumin. Fibrates also increase cholesterol excretion into the bile, leading to a risk of cholelithiasis. In patients with suspected cholelithiasis, diagnostic studies should be conducted; if gallstones are found, fibrate therapy should be discontinued [109].

STATINS

Mechanism of Action and Clinical Pharmacology

HMG-CoA reductase inhibitors, usually known as statins, are the most effective and the most prescribed class of lipid-lowering drugs. Statins selectively inhibit HMG-CoA reductase, the enzyme responsible for the conversion of HMG-CoA to mevalonate, the rate-limiting step in cholesterol synthesis in the liver [109]. Inhibition of HMG-CoA reductase leads to increased expression of the hepatic LDL receptor and increased clearance of LDL from the circulation [235]. Statins are the primary pharmacotherapeutic agents used to lower LDL cholesterol levels.

The first statin to be tested and approved for clinical use, lovastatin, was isolated from the mold *Aspergillus terreus*, and pravastatin and simvastatin are chemically modified derivatives of the original molecule. Atorvastatin, fluvastatin, and rosuvastatin are synthetic compounds with distinct molecular structures. Lovastatin, pravastatin, and simvastatin are inactive prodrugs that require hydroxylation in the liver into their active forms. Although all statins are clinically very effective, rosuvastatin, atorvastatin, and simvastatin have the highest drug efficacy in this class (***Table 5***).

The selective inhibition of hepatic HMG-CoA reductase initiates a cascade of events that results in decreased synthesis of cholesterol; decreased liver release of VLDL; and activation of the transcription factor SREBP2, which upregulates the LDL receptor and consequently increases the clearance of plasma LDL. As 60% to 70% of serum cholesterol is synthesized in the liver by HMG-CoA reductase, inhibition of this enzyme drastically lowers circulating LDL [142].

In addition to the lipid-lowering actions of statins, studies suggest that the drugs are also implicated in a number of additional actions known as pleiotropic effects. This includes modulation of endothelial function, decrease in vascular inflammation, neuroprotection, and immunomodulation by inhibition of major histocompatibility complex II expression, which is upregulated in patients with myocarditis, multiple sclerosis, and rheumatoid arthritis [143; 144; 145]. Statins have been linked to a reduction in the risk of developing Alzheimer disease independent of the drugs' lipophilicity [145; 146].

As stated, the percentage reduction in LDL levels is used to estimate the efficacy of statin therapy, with the primary goal being a ≥ 50% reduction [24]. In clinical practice, absolute responses in LDL levels to statin therapy depend on baseline levels and the intensity (i.e., low, moderate, or high) of lipid-lowering therapy [24].

In addition to efficacy, therapeutic goals, and patient preferences, the clinical choice of a statin also considers cost and drug safety. Lovastatin, simvastatin, and pravastatin have all been shown to be safe in clinical trials involving thousands of subjects for five or more years. This should be particularly taken into account when treating younger patients.

The combination of statins with other lipid-lowering drugs further improves the lipid-lowering outcome. The combination of simvastatin with ezetimibe lowers LDL by an additional 18% to 20% compared with simvastatin alone [147]. Administration of a statin with a bile acid-binding resin (e.g., cholestyramine, colestipol) produces 20% to 30% greater reductions in LDL than statins alone [148; 149].

Statins are well absorbed through the gastrointestinal system and are metabolized in the liver by cytochrome P450. Metabolites are eliminated through the bile and excreted in the feces and, to a much lesser extent, by the kidneys. These drugs should not be used in patients with active liver disease and should be used cautiously at lower doses in patients with kidney disease [109].

Statins are effective in the prevention of ASCVD [67; 150; 151]. In a 2009 review and meta-analysis, these drugs are referred to as "the most important advance in stroke prevention since the introduction of aspirin and antihypertensive

STATIN DOSES REQUIRED TO REDUCE LDL TO BASELINE GOAL						
Agent	**Percent Reduction in LDL Necessary to Reach Goal**					
	20% to 25%	**26% to 30%**	**31% to 35%**	**36% to 40%**	**41% to 50%**	**51% to 55%**
Rosuvastatin	–	–	–	5 mg	10 mg	20–40 mg
Atorvastatin	–	–	10 mg	20 mg	40 mg	80 mg
Simvastatin	–	10 mg	20 mg	40 mg	80 mg[a]	–
Lovastatin	–	20 mg	40 mg	80 mg	–	–
Pravastatin	10 mg	20 mg	40 mg	80 mg	–	–
Fluvastatin	20 mg	40 mg	80 mg	–	–	–
Pitavastatin	–	1–4 mg	–	–	–	–
[a]Increasing to 80 mg is not routinely recommended. Reserve for patients who have been taking this dose for more than 12 consecutive months without evidence of myopathy.						
Source: [14; 24; 109; 141]						*Table 5*

treatments" [152]. Analysis of the risk-benefit ratio of statins after one year of treatment reveals that an estimated 1,587 cases of fatal and non-fatal cases of ASCVD were prevented against 3.4 cases of rhabdomyolysis [140; 153; 154]. Randomized controlled trials across differing risk categories of patients have shown that statins confer significant relative risk reductions in cardiovascular events and all-cause mortality [235].

Adverse Effects

Dizziness (7%), diarrhea (4.5%), nausea/vomiting (3%), and abdominal cramps (3%) are among the most frequently reported adverse effects. Statins are contraindicated during pregnancy and lactation [128].

Statins are associated with hepatotoxicity and elevated transaminases in 1% to 2% of patients [128]. However, in 2014, the FDA concluded that the rate of liver injury associated with statin use is rare enough that routine liver enzyme screening while using statins is not needed. It is recommended that liver enzyme tests be performed before statin use begins and then only if there are symptoms of liver damage, including extreme fatigue, loss of appetite, right upper abdominal discomfort, dark urine, or jaundice [155; 156].

The FDA has also noted a small increase in the risk for type 2 diabetes while taking statins. It is noted that there may be a need to assess blood sugar levels after beginning statin use, especially in those with other risk factors [156].

The incidence of myopathy, characterized by muscle pain, weakness, and grossly elevated creatine kinase levels (>10 times the upper limit of normal), with the use of a statin alone is reported in 0.1% to 0.2% of patients [128]. Yet, studies have indicated that the occurrence of statin-induced myopathy may be much higher than originally reported, as high as 10% to 15% of patients treated with statins [140; 157].

A deficiency in coenzyme Q10 (CoQ10), a product of the HMG-CoA reductase pathway selectively inhibited by statins, has been proposed as a possible mechanism of statin-related myotoxicity. Although CoQ10 serum levels are below normal in patients taking statins, there is no direct correlation between myotoxicity and CoQ10 levels in muscle cells. Furthermore, studies of supplementation with CoQ10 to prevent myopathy in patients taking statins have not found conclusive evidence of effectiveness [140; 158; 159; 160]. Alternatively, other studies have shown that the inhibition of HMG-CoA reductase by statins inhibits mitochondrial function, increases intracellular calcium, and activates apoptosis (i.e., programmed cell death) [161]. This latter mechanism is being further investigated and may play a crucial role in the development of lipid-lowering drugs with an even higher safety profile [140].

The occurrence of rhabdomyolysis, defined as skeletal muscle necrosis with release of potentially toxic muscle cell components into the general circulation, has been rarely reported. Possible complications of rhabdomyolysis include myoglobinuric acute renal failure, disseminated intravascular coagulation, hyperkalemia, and cardiac arrest.

The risk of myopathy or rhabdomyolysis increases with higher statin plasma levels, which can be the result of higher doses, decreased hepatic clearance, or drug interactions [109; 156; 162].

The AHA/ACC recommend that a clinician-patient risk discussion be conducted prior to the initiation of statin therapy to review and weigh the risk reduction benefit against the potential for adverse effects, drug-drug interactions, and safety. Patients with statin-associated muscle symptoms should be evaluated for nonstatin causes and predisposing factors. When a statin is indicated, identify predisposing factors for statin-associated side effects (e.g., new-onset diabetes mellitus, muscle symptoms) prior to initiating statin therapy (***Table 6***) [24].

AHA/ACC RECOMMENDATIONS FOR STATIN SAFETY AND MANAGEMENT OF STATIN-ASSOCIATED SIDE EFFECTS
In patients with nonsevere statin-associated side effects, reassess and rechallenge to achieve maximal LDL lowering by modified dosing regimen, alternate statin, or in combination with nonstatin therapy (Class I, based on moderate-quality evidence).
In patients with increased diabetes risk or new-onset diabetes, continue statin therapy with added emphasis on adherence, net clinical benefit, and core principles of healthy lifestyle (Class I, based on moderate-quality evidence).
In patients treated with statins, measure creatine kinase levels in individuals with severe SAMS and objective muscle weakness. Measure liver transaminases as well as total bilirubin and alkaline phosphatase (hepatic panel) if symptoms suggest hepatotoxicity (Class I, based on limited data).
In patients at increased ASCVD risk with chronic, stable liver disease (including non-alcoholic fatty liver disease), when appropriately indicated, it is reasonable to use statins after obtaining baseline measurements and determining a schedule of monitoring and safety checks (Class I, based on moderate-quality evidence).
In patients at increased ASCVD risk with severe SAMS or recurrent SAMS despite appropriate statin rechallenge, it is reasonable to use randomized controlled trial-proven nonstatin therapy that is likely to provide net clinical benefit (Class IIa, based on moderate-quality evidence).
SAMS = statin-associated muscle symptoms.
Source: [24] *Table 6*

Drug Interactions

Statins have pharmacokinetic interactions with drugs that inhibit their metabolism and increase their bioavailability, such as CYP3A4 inhibitors (e.g., azole antifungals, erythromycin, protease inhibitors, amiodarone, grapefruit) and CYP2C9 inhibitors (e.g., NSAIDs, phenytoin, warfarin), as well as drugs that potentiate statins' therapeutic and adverse effects (e.g., fibrates, niacin). These interactions increase statin toxicity [67; 128; 163]. Interaction between statins and fibrates, particularly with gemfibrozil, increases the risk of rhabdomyolysis. For this reason, fenofibrate is preferred when the two classes are combined [140].

Clinical Outcome

Statins, the most potent lipid-lowering drugs, are indicated in a variety of clinical conditions and are effective in the prevention of ASCVD and stroke. They lower LDL in a dose-dependent manner by 20% to 55% and are accepted as the drug of choice in the treatment of elevated LDL. They are also effective in the treatment of hypertriglyceridemias when levels are greater than 250 mg/dL, although fibrates remain the drug of choice for hypertriglyceridemias. When elevation of HDL is required, niacin remains the drug of choice, although co-administration of statins and niacin may be considered in patients who also have an elevated LDL. Co-administration of statins and niacin, fibrates, or ezetimibe increases the lipid-lowering benefit but also increases the risk for adverse effects. Furthermore, randomized controlled trials do not support the use of fibrates and niacin as add-on drugs to statin therapy. However, if a fibrate is necessary in a patient being treated with a statin, it is safer to use fenofibrate than gemfibrozil due to lower risk of severe myopathy [24]. These patients should be carefully monitored.

In patients taking statins who develop myopathy and creatine kinase levels 10 or more times higher than normal, immediate discontinuation of the drug is recommended. Dietary therapy and lifestyle changes should be implemented and other lipid-lowering drugs, such as niacin, fibrates, and bile-acid sequestrants, should be considered. The National Lipid Association Muscle Expert Panel guidelines recommend considering the re-introduction of low doses of statins in conjunction with ezetimibe in cases in which the lipid-lowering benefit of statins outweighs the risk of myopathy [140; 164].

The more LDL is reduced on statin therapy, the greater will be subsequent risk reduction. Therefore, the ACC/AHA recommend patients with clinical ASCVD be treated with a maximally tolerated statin to lower LDL levels by ≥50%.

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Level of Evidence: I (Strong)

NICOTINIC ACID DERIVATIVES

Mechanism of Action and Clinical Pharmacology

Niacin, also known as nicotinic acid or vitamin B3, is a water-soluble vitamin that at physiologic levels is a substrate for nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP), important cofactors in intermediary metabolism. Niacin is available in normal- or extended-release formulation as well as in conjunction with lovastatin (as Advicor).

The lipid-lowering and vasodilatory effects of niacin are not related to its vitamin properties. The discovery that the vasodilatory properties of niacin result from its binding to a G protein-coupled receptor (GPR109A) expressed in blood vessels has allowed for better understanding of the mechanisms underlying its metabolic and vascular effects [165]. In addition, further evidence suggests that the lipid-lowering effects result from niacin binding to another G protein-coupled receptor on adipocytes that inhibits lipoprotein lipase and prevents triglyceride release from chylomicrons. The vasodilatory effect of niacin, on the other hand, involves the release of vasodilatory prostaglandins D2 and E2 [30].

It is relevant to emphasize that niacinamide, a nicotinic acid derivative usually preferred as a vitamin supplement, has neither lipid-lowering nor vasodilatory properties [30; 166]. The lipid-lowering effects of niacin require a dose of 1,500 – 3,000 mg/day, whereas the recommended vitamin dose is 50 mg/day.

Niacin has low cost, a long history of clinical trials, and extensive use as a safe lipid-lowering drug, supported by evidence that it is effective in the prevention of ASCVD [31]. However, it is no longer recommended, except in specific clinical situations, such as a patient with triglyceride levels >500 mg/dL, a patient who is not able to achieve desired response, or a patient with intolerance to other therapies [109]. Although niacin has a mild LDL-lowering action, randomized controlled trials do not support its use as an add-on to statin therapy, and it is not listed as an LDL-lowering drug option in the 2018 AHA/ACC guideline [24]. Niacin has not been shown to reduce ASCVD outcomes beyond that achieved with statin use, and it may be associated with harm [167; 168; 169].

FISH OIL DERIVATIVES

Mechanism of Action and Clinical Pharmacology

A 1975 study conducted by Danish scientists showed that the composition of plasma lipids (e.g., cholesterol esters, triglycerides, phospholipids) varied considerably in the Inuit population of Greenland when compared both to the European Danish and to Inuit living in Denmark [170]. Interestingly, epidemiologic studies showed that Inuit living in Greenland following a traditional diet rich in fat had a lower mortality from ASCVD than Inuit living in Denmark who followed a Western diet. This puzzling observation is known as the "Eskimo paradox" [171]. It is now well established that, although individual genetic background plays an important role in the development of ASCVD, the answer is the type of dietary fat consumed. Greenland Inuit consume a traditional diet rich in omega-3 fatty acids from fish and fish-eating mammals (seal and whale) rather than a diet poor in omega-3 sources such as the traditional Western diet [172].

Omega-3 polyunsaturated fatty acids are considered essential fatty acids because humans, as well as other mammals, are unable to synthesize these compounds efficiently. Eicosapentaenoic (EPA) and docosahexaenoic acids (DHA) are omega-3 polyunsaturated fatty acids derived from alpha-linolenic acid (ALA). Although humans are able to transform negligible amounts of ALA into EPA and DHA (<1%), dietary supplementation is the only physiologically relevant source [173]. Omega-3 fatty acids EPA and DHA are abundant in fatty fish, such as salmon, mackerel, sardines, trout, and herring, and other seafood sources, as well as in walnuts and canola, flaxseed, and linseed oils. Vegetable oils such as soybean, corn, sunflower, safflower, and cotton seed oils are good dietary sources of omega-6 fatty acids, which will be discussed in detail later in this course [57; 174; 175; 176].

Although the mechanism of action of omega-3 fatty acids is not yet completely understood, both preclinical and clinical studies provide solid evidence that EPA and DHA both reduce the synthesis and secretion of VLDL and increase triglyceride removal from VLDL and chylomicrons through the upregulation of lipoprotein lipase [177]. The distinct mechanisms of action of omega-3 fatty acids differ from other lipid-lowering drugs, which helps to explain why they have complementary lipid benefits when administered with statins [173]. Omega-3 fatty acids also have well established antiarrhythmic, antihypertensive, anti-atherogenic, and antithrombotic properties [173; 178; 179; 180; 181; 182; 183].

Omega-3 fatty acids are effective in primary and secondary prevention of CHD, reduce the risk of sudden cardiovascular mortality by 45%, and provide a 20% relative risk reduction in overall mortality [175; 180; 184; 185; 186; 187; 188]. EPA and DHA omega-3 fatty acids lower triglycerides by 20% to 50% and were approved by the FDA in 2004 as adjunct to the diet for the treatment of very high triglyceride levels (≥500 mg/dL or 5.65 mmol/L) [189]. The effects on LDL seem to vary among studies from moderate dose-dependent increases to decreases in LDL. A moderate increase in HDL (5% to 10%) is more consistently reported [173; 190; 191]. As a result, omega-3 fatty acids are used in the treatment of hypertriglyceridemias, either alone or in conjunction with other lipid-lowering drugs.

Omega-3 fatty acids are readily available as dietary supplements in the United States. It is important to note that dietary supplements are not FDA-required to demonstrate safety and efficacy prior to marketing, whereas prescription products are. Dietary supplements generally contain lower levels of EPA and DHA than prescription products, are not approved or intended to treat disease, and may have levels of EPA and DHA that vary widely within and between brands. Supplements should not be substituted for prescription products, as they may also contain unwanted cholesterol or fats or potentially harmful components, including toxins and oxidized fatty acids [192].

Omega-3 fatty acids also are readily available in the United States as prescription medications. One prescription medication is comprised of 900 mg of ethyl esters of omega-3 fatty acids, a combination of EPA (approximately 500 mg) and DHA (approximately 400 mg) [189]. A second available medication consists of 1,000 mg omega-3 in free fatty acid form, which is intended to improve the bioavailability [193]. This drug contains approximately 500 – 600 mg EPA, 150 – 250 mg DHA, and 150 – 350 mg other omega-3 fatty acids. Drug labeling dosage information indicates a dose of 4 g/day, taken as a single 4-g

dose (four capsules) or as two 2-g doses (two capsules twice daily) [189]. In one study, a minimum dose of 500 mg per day of combined EPA/DHA was recommended for individuals without underlying overt ASCVD, and 800-1,000 mg/day was recommended for individuals with CHD and heart failure [194]. A 2009 review validated the beneficial effects of EPA/DHA alone or in conjunction with fibrates in the reduction of triglycerides. It also further corroborated the safety profile of omega-3 polyunsaturated fatty acids [195]. In 2019, the FDA approved icosapent ethyl, a prescription omega-3 fatty acid, as an adjunctive therapy (to maximally tolerated statin therapy) to reduce the risk of cardiovascular events in adults with elevated triglyceride levels (≥150 mg/dL), cardiovascular disease and/or diabetes, and at least two additional risk factors [232].

The omega-3 fatty acids EPA and DHA are safe and cost effective and are indicated as an adjunct to diet in patients with hypertriglyceridemias [109; 189]. They may be considered for triglyceride levels >1,000 mg/dL and may be used alone or in conjunction with HMG-CoA reductase inhibitors [109]. Omega-3 fatty acids are effective in the prevention of ASCVD. Their effect on cardiovascular morbidity and mortality has not been determined [189].

Adverse Effects

Omega-3 fatty acids are remarkably well tolerated. Minor gastrointestinal symptoms (e.g., fishy aftertaste, eructation, diarrhea) may be observed in a dose-related manner [189]. Clinical trials have concluded that omega-3 fatty acids do not have adverse effects on plasma glucose levels, bleeding, levels of muscle or liver enzymes, or kidney or nerve function.

Contaminants such as methylmercury, polychlorinated biphenyls, and dioxins may be concentrated in certain species of fish, such as shark, swordfish, king mackerel, and golden snapper. The FDA and the Environmental Protection Agency have issued a statement advising women who are or may become pregnant, breastfeeding mothers, and young children to avoid eating some types of fish and to eat fish and shellfish that are lower in mercury [196]. However, the levels of contaminants in omega-3 fatty acids, either as generic supplements or in the ethyl ester formulation, are well below acceptable levels of toxicity due to extensive purification processes. In April 2009, the FDA posted a warning regarding the ethyl ester formulations of omega-3 fatty acids reporting anaphylactic or severe allergic reactions (i.e., rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue) and hemorrhagic diathesis [197].

Drug Interactions

Due to their antiplatelet effect, omega-3 fatty acids may increase bleeding time in a dose-dependent manner [109; 189]. However, no cases have been reported, even when administered at high doses alone or in combination with anticoagulant medications. In patients receiving anticoagulant medication, it has been recommended that bleeding times be monitored during the first three to six months, the time normally required for omega-3 fatty acids to reach their maximum clinical effect.

STEROLS AND STANOLS

Mechanism of Action and Clinical Pharmacology

Plant sterols and stanols, also known as phytosterols, are bioactive compounds structurally and physiologically similar to cholesterol. Sterols are present naturally in small quantities in many fruits, vegetables, nuts, seeds, cereals, legumes, vegetable oils, and other plant sources, and stanols occur in even smaller quantities in many of the same sources [57; 173; 174; 175; 176; 198; 199].

Omega-6 polyunsaturated fatty acids such as gamma-linoleic acid (GLA) are derived from linoleic acid. Omega-9 polyunsaturated fatty acids, unlike omega-3 and omega-6, are non-essential because they can be synthesized in humans. The most relevant omega-9 fatty acid is oleic acid, which is present in olive oil, and supplementation is not required.

The lipid-lowering properties of omega-6 polyunsaturated fatty acids, and linoleic acid in particular, are related to their ability to alter various steps of the intestinal absorption of cholesterol. Specifically, they downregulate the intestinal expression of the cholesterol transporter NPC1L1, compete with cholesterol for binding to NPC1L1, lower the cholesterol esterification rate by ACAT2, decrease the amount of cholesterol secreted via the chylomicrons, and upregulate the expression of ATP-binding cassette-transporters ABCG5 and ABCG8 in intestinal cells, which may result in an increased excretion of cholesterol by the enterocyte back into the lumen [199].

The beneficial role played by omega-6 polyunsaturated fatty acids in the prevention of CHD results from their transformation into anti-inflammatory and vasodilatory eicosanoids, such as prostacyclin and lipoxin A4. Some studies, however, have recommended dietary reductions in omega-6 intake, based on the potential risk of increased transformation of omega-6 into pro-inflammatory, vasoconstrictive, pro-platelet aggregation eicosanoids, such as prostaglandin E2, thromboxane A2, and leukotriene B4. An advisory of the AHA has concluded that [200]:

Aggregate data from randomized trials, case-control and cohort studies, and long-term animal feeding experiments indicate that the consumption of at least 5% to 10% of energy from omega-6 polyunsaturated fatty acids reduces the risk of CHD relative to lower intakes. The data also suggest that higher intakes appear to be safe and may be even more beneficial (as part of a low-saturated-fat, low-cholesterol diet). In summary, the AHA supports an omega-6 polyunsaturated fatty acid intake of at least 5% to 10% of energy in the context of other AHA lifestyle and dietary recommendations. To reduce omega-6 polyunsaturated fatty acid intakes from their current levels would be more likely to increase than to decrease risk for CHD.

Adverse Effects

No serious side effects have been reported with omega-6 fatty acids. Some minor gastrointestinal effects may resemble those described for the omega-3 polyunsaturated fatty acids. Plant

sterols and stanols lower plasma levels of beta-carotene by 25% and vitamin E by 8% [201].

Drug Interactions

Bile acid sequestrants and additives and drugs that impair the absorption of fat and soluble nutrients, such as olestra and orlistat, have the potential to significantly impair absorption of omega-3, 6, and 9 polyunsaturated fatty acids.

ADENOSINE TRIPHOSPHATE-CITRATE LYASE (ACL) INHIBITOR

Mechanism of Action and Clinical Pharmacology

As noted, in 2020, the FDA approved bempedoic acid for the treatment of Heterozygous familial hypercholesterolemia or established ASCVD [233]. Bempedoic acid is the first in the class of adenosine triphosphate-citrate lyase (ACL) inhibitors. By inhibiting ACL, a hepatic enzyme involved in the synthesis of cholesterol, bempedoic acid decreases the conversion of mitochondrial-derived citrate to cytosolic ACL, creating less substrate for cholesterol and fatty acid synthesis. This ultimately decreases liver cholesterol synthesis and decreases serum LDL-C levels by upregulating LDL receptors [239].

Bempedoic acid is available as monotherapy and in a tablet with ezetimibe as combination therapy. It is an option to modify statin therapy or for patients who cannot tolerate statins. This combination has been demonstrated in clinical trials to lower LDL-C levels by 36% and, when given as monotherapy, bempedoic acid and ezetimibe have been respectively shown to lower LDL-C levels by 15% to 23% and by 13% to 20%, respectively [239]. The usual dose is 180 mg bempedoic acid and, if used, 10 mg ezetimibe once daily.

Adverse Effects

Potential adverse effects associated with bempedoic acid include leukopenia, thrombocythemia, upper respiratory tract infection, and, most commonly, hyperuricemia and gout. Gout and hyperuricemia are more common at higher doses and related to inhibition of tubular OAT2, which may increase blood uric acid levels [109]. It usually develops within the first four weeks of treatment initiation and persists until cessation of administration.

Rupture or injury of tendon has rarely (<1%) occurred, typically involving the rotator cuff, biceps tendon, or Achilles tendon [109]. Risk factors include age older than 60 years, concomitant use of corticosteroids or fluoroquinolones, kidney failure, and prior tendon disorders.

Drug Interactions

Bempedoic acid can increase the serum concentration of certain drugs metabolized by the liver, including elagolix, voxilaprevir, and asunaprevir and should be avoided in patients taking these medications [109]. It may also increase the serum levels of the statins simvastatin and lovastatin. If bempedoic acid is coadministered with these agents, the dose should be limited to no more than 20 mg daily for simvastatin or 40 mg daily for lovastatin [109; 239].

NOVEL PHARMACOTHERAPIES FOR HYPERLIPIDEMIAS

The discovery of lipid-lowering drugs has been a major contribution to the clinical management of hyperlipidemias and the prevention of ASCVD. However, the incidence of lipid disorders and resultant cardiovascular pathology continues to increase worldwide.

Existing available therapies are generally effective. Statins are the most prescribed lipid-lowering drugs because of their therapeutic efficacy and beneficial effects on the prevention of ASCVD, although the potential for the occurrence of serious adverse effects in a small number of patients requires monitoring. Other therapies, including bile acid-binding resins, ezetimibe, fibrates, niacin, and omega-3 polyunsaturated fatty acids, either alone or co-administered with other lipid-lowering drugs, including statins, can further lower LDL and triglycerides or raise HDL. However, patients with severe hypercholesterolemia or those intolerant to statins may not attain the recommended targets with available regimens. In fact, it is estimated that 10% of patients are not able or cannot tolerate available therapies to achieve recommended LDL goals [140]. So, continued research for globally effective pharmacotherapy is underway.

Advances in pharmacologic research have provided new molecular insights on lipid metabolism, and translational knowledge is being applied to the development of novel therapies including squalene synthase inhibitors (e.g., lapaquistat), new generation cholesterol absorption inhibitors, ATP-binding cassette transporter activators/cholesterol excretion stimulators, a new generation of nicotinic acid analogs, microsomal triglyceride transfer protein inhibitors, antisense oligonucleotides against Apo B-100 (e.g., mipomersen), and PCSK9, a serine protease synthesized in the liver, being investigated for its regulatory effect on LDL receptors [56; 202; 203; 204; 205; 206].

Squalene synthase modulates the first committed step of hepatic cholesterol biosynthesis. Its inhibition results in a reduction in cholesterol synthesis in the liver and upregulation of the LDL receptor. Inhibition of squalene synthase activity occurs downstream from HMG-CoA reductase inhibited by statins. Theoretically, squalene synthase inhibitors reduce LDL cholesterol without causing the myopathy side effect seen with upstream inhibition of HMG-CoA. As of 2013, only one synthase inhibitor, lapaquistat (TAK-475), has undergone extensive development in clinical trials as a monotherapy; however, two cases of severe liver enzyme elevations among more than 5100 study participants exposed to the drug resulted in termination of the development program [207; 208].

New-generation cholesterol absorption inhibitors (e.g., AVE5530) share some mechanistic properties with ezetimibe, a NPC1L1 transporter inhibitor. However, rather than being partially absorbed in the intestine, they remain in the lumen where they can exert their pharmacologic actions more effec-

tively than ezetimibe. As a result, these agents can inhibit cholesterol absorption for up to 24 hours [209]. These drugs have been subjected to clinical trials. To date, four trials have been terminated and one completed, with results not yet available [210].

The process of cholesterol being transported back into the intestinal tract by selective transporters, such as the ATP-binding cassette transporters, has also been a target for potential treatments [55]. A new generation of drugs that is able to stimulate the ATP-binding cassette transporter and promote cholesterol elimination by enterocytes is being investigated [56].

The discovery of a G protein-coupled receptor for nicotinic acid has provided new insights on its lipid-lowering properties. This has raised the possibility of developing selective agonists that will not share its flush-inducing side effects [165; 203].

Microsomal triglyceride transfer protein catalyzes the assembly of cholesterol, triglycerides, and Apo B-100. Microsomal triglyceride transfer protein inhibitors (e.g., AEGR-733, lomitapide) inhibit intestinal assembly of chylomicrons and hepatic synthesis of VLDL, consequently lowering LDL. Initial clinical results showed a dose-dependent reduction of LDL by 19% to 30% when administered alone, or by 46% when administered in combination with ezetimibe [211]. Research is ongoing [212; 213].

Antisense oligonucleotides (e.g., mipomersen) are single-stranded DNA that bind to matching mRNA and induce its selective degradation. Pre-clinical studies and small clinical trials have shown a 30% to 50% reduction in LDL with the use of these agents. Increases in transaminases and injection site reactions have been observed, and larger clinical trials are being conducted [210; 214].

Downregulation of the LDL receptor by PCSK9 is one regulatory mechanism that controls plasma LDL cholesterol concentrations. Studies have demonstrated that the PCSK9 enzyme binds to the hepatic LDL receptor and promotes its degradation, which in turn decreases LDL uptake and increases plasma LDL cholesterol levels. However, PCSK9 may have much broader roles than initially thought. For example, when human PCSK9 is injected into LDL receptor-deficient mice, it is still rapidly cleared by the liver, suggesting that it is physiologically also cleared by receptors other than the LDL receptor [215; 216; 217; 218].

PCSK9 inhibitors are monoclonal antibodies that inactivate the PCSK9 enzyme and promote clearance of LDL from the circulation. Administration of PCSK9 inhibitors can reduce serum LDL cholesterol by 60% [235]. In 2015, the FDA approved two PCSK9 inhibitors, alirocumab and evolocumab, to be used in conjunction with diet and statin therapy to reduce LDL cholesterol. To date, clinical trials of PCSK9 inhibitor therapy as an adjunct to statins have been conducted for secondary prevention of ASCVD in high-risk patients [235]. The demonstrated benefit is modest, the cost relatively high, and the long-term safety not yet well-established.

ROLE OF LIPID-LOWERING DRUGS IN THE PREVENTION OF ASCVD MORBIDITY AND MORTALITY

As discussed, the clinical approach to hyperlipidemias is aimed at the primary and secondary prevention of ASCVD. As the evidence has shown, it is clear that lipid-lowering strategies play a fundamental role in the primary prevention of ASCVD. Primary prevention is defined as the long-term management of individuals at increased risk for but without clinical evidence of ASCVD and who have not undergone revascularization procedures [220]. Secondary prevention is defined as the clinical management of individuals with a history of ASCVD.

Primary prevention of hyperlipidemias aims to avert new onset CHD and is considered an important aspect of the societal approach to the promotion of cardiovascular health [25]. The goal of primary prevention is to assess and reduce risk factors for CHD in each age group and to emphasize adherence to a healthy lifestyle. This is achieved through two complementary approaches: population strategies and clinical "individual" strategies [24]. Population (public health) strategies shift the distribution of risk factors of the target population to more desirable levels. For example, the 2018 AHA/ACC guideline emphasizes promotion of a heart-healthy lifestyle that improves cardiovascular health and prevents dyslipidemia and other ASCVD risk factors for all age groups. Successful implementation of these recommendations on a population level requires the multidisciplinary team of healthcare providers to help bridge the gap between public health and patient management by supporting and advocating for continued public health initiatives and by encouraging a collaborative effort among healthcare professionals, government agencies, schools, the food industry, and the media [25].

Healthcare delivery is complex, and barriers to guideline implementation can occur at both the public and individual level (***Table 7***) [24].

The effectiveness of primary prevention on the cholesterol levels of aging patients has been validated by the slower rate of increase in cholesterol levels associated with aging in patients for whom primary prevention strategies have been implemented [23; 25; 221]. Attaining lower LDL and triglyceride plasma concentrations can be achieved by a combination of lifestyle changes and drug therapy. As stated, the 2018 AHA/ACC guideline continues to emphasize the adoption of a heart-healthy lifestyle from adolescence onward, as this reduces ASCVD risk at all ages. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome [24].

Secondary prevention should be initiated in patients with clinical ASCVD. A meta-analysis of randomized controlled trials conducted by the Cholesterol Treatment Trialists demonstrated that lowering LDL with statins reduces major ASCVD events and also benefits patients with stroke or peripheral artery disease [222; 223]. Compared with moderate-intensity statin therapy, high-intensity statin therapy significantly reduced major vascular events by 15% with no significant reduction

AHA/ACC RECOMMENDATIONS TO IMPROVE ADHERENCE TO GUIDELINE IMPLEMENTATION
Provide interventions focused on improving adherence to therapy (e.g., telephone reminders, calendar reminders, integrated multidisciplinary educational activities, pharmacist-led interventions) (Class I, based on high-quality evidence).
Identify patients not receiving guideline-directed medical therapy, and facilitate initiation of appropriate guideline-directed medical therapy using multifaceted strategies to improve guideline implementation (Class I, based on moderate-quality evidence).
Conduct patient-clinician discussion prior to therapy to promote shared decision-making (Class I, based on moderate-quality evidence).

Source: [24] *Table 7*

in coronary deaths. High-intensity statin therapy generally reduces LDL levels by ≥ 50%. However, as stated, absolute benefit depends on baseline levels [24]. Lifestyle changes provide only moderate improvement of the lipid profile in patients with previous ASCVD, so although they should be implemented, pharmacotherapy is required to attain therapeutic goals [23; 24].

The complexity of health status in patients with a history of ASCVD requires an approach of multifactorial risk reduction. Multifactorial risk reduction has a synergistic effect on disease progression and clinical outcomes and should be associated with a case management approach [23; 224; 225]. Case management allows for collaborative and effective expert evaluation, systematic intervention, and regular follow-up. Management should focus not only on the appropriate drug choices but also on patient education and counseling [23; 24; 225; 226].

CLINICAL ASSESSMENT OF RISK ASSOCIATED WITH HYPERLIPIDEMIAS

The Framingham Heart Study took the lead in creating risk-prediction equations, and previous guidelines made use of the Framingham risk score algorithm. However, the 2013 Work Group for the guideline on assessment of cardiovascular risk decided against using the Framingham algorithm due to its use of an exclusively white sample population and the limited scope of the outcome (i.e., to determine CHD alone) [227]. Instead, the Group compiled data from five community-based cohorts that were broadly representative of the U.S. population. The final pooled cohorts included participants from several large, racially and geographically diverse, NHLBI-sponsored studies. The Group validated pooled cohort equations that provided sex- and race-specific estimates of 10-year risk of first, hard ASCVD event (i.e., MI and stroke, fatal and nonfatal) for African-American and white men and women 40 to 79 years of age (***Table 8***). Variables included in the risk equation were age, total cholesterol, HDL, systolic blood pressure, diabetes, and current smoking status [227].

Data from the Women's Health Initiative initially appeared to indicate that the pooled cohort equations overestimated the risk of ASCVD, but when event surveillance was improved by data from Centers for Medicare and Medicaid Services, it was found that the equations discriminated risk well [228]. However, because the algorithms may over- or underestimate risk for individual patients, the 2013 AHA/ACC guideline on assessment of cardiovascular risk additionally introduced the clinician-patient risk discussion to facilitate decisions about appropriate therapy. This risk discussion is an integral part of the decision-making process in the 2018 AHA/ACC guideline on the management of blood cholesterol [24; 227].

As stated, the pooled cohort equations estimate risk of hard ASCVD events among patients 40 to 79 years of age who are without pre-existing disease. Because pooled cohort equations are population equations, the estimates and recommendations for therapy should be considered in the context of the patient's individual circumstances. Patients are considered to be at elevated risk if the pooled cohort equations estimate is ≥ 7.5% [24].

The 2018 and 2019 AHA/ACC guidelines concur with the recommendation that clinical management should be based on calculation of the patient's 10-year estimated risk of ASCVD, as this will influence the intensity of management, whether it be lifestyle modification, drug therapy, or both [24; 236]. In children, adolescents, and young adults, priority should be estimation of lifetime risk and promotion of lifestyle risk reduction [24]. The ACC ASCVD risk assessment tool is available (http://tools.acc.org/ASCVD-Risk-Estimator-Plus) to estimate the risk of ASCVD within 10 years. The risk calculator is intended for use in patients 40 to 75 years of age who do not have diabetes and whose LDL cholesterol is 70 – 189 mg/dL [235].

The AHA/ACC recommends that for adults 40 to 70 years of age, clinicians routinely assess traditional risk factors and calculate the estimated 10-year risk of ASCVD [24; 236]. For adults 20 to 39 years of age, clinicians should assess (monitor) ASCVD risk factor status every three to six years. For adults at borderline risk (5% to <7.5% 10-year ASCVD risk) or intermediate risk (7.5% to <20% 10-year ASCVD risk), additional risk-enhancing factors can be used to guide decisions about therapeutic interventions; such factors may include family history of premature ASCVD, chronic inflammatory disease (e.g., rheumatoid arthritis, lupus), chronic kidney disease, early menopause, or metabolic syndrome. In adults at intermediate

DISTRIBUTION OF ESTIMATED 10-YEAR RISK OF FIRST HARD ASCVD EVENT IN ASCVD-FREE NONPREGNANT U.S. POPULATION, 40 TO 79 YEARS OF AGE, BY SEX AND RACE/ETHNICITY[a]							
Population	**Predicted 10-Year Risk of ASCVD Event**						
	<2.5%	**2.5% to 4.9%**	**5.0% to 7.4%**	**7.5% to 9.9%**	**10.0% to 14.9%**	**15.0% to 19.9%**	**≥20.0%**
Total	33.4%	21.0%	12.7%	7.4%	8.9%	6.3%	10.2%
All Races/Ethnicities							
Men	17.4%	22.7%	15.6%	10.1%	12.1%	8.8%	13.3%
Women	48.0%	19.5%	10.0%	5.0%	5.9%	4.1%	7.5%
White Race/Ethnicity							
Men	18.0%	22.4%	15.7%	10.0%	11.7%	8.7%	13.6%
Women	47.1%	20.4%	10.7%	5.1%	5.5%	4.1%	7.1%
African American Race/Ethnicity							
Men	1.4%	23.9%	20.6%	11.8%	17.4%	11.1%	13.8%
Women	36.5%	18.7%	10.9%	6.5%	9.4%	5.7%	12.3%
Hispanic Race/Ethnicity							
Men	24.0%	22.1%	13.2%	10.6%	11.4%	6.2%	12.6%
Women	59.4%	14.5%	7.5%	4.5%	4.9%	3.0%	6.3%
Other Race/Ethnicities							
Men	20.8%	27.1%	11.6%	7.2%	11.5%	12.3%	9.4%
Women	59.8%	18.6%	4.4%	1.7%	6.4%	2.4%	6.7%
[a]Data derived by applying pooled cohort equations to National Health and Nutrition Examination Surveys, 2007–2010.							
Source: [227]							*Table 8*

risk or borderline 10-year ASCVD risk, if risk-based decisions for preventive therapy such as statin treatment remain uncertain, it is reasonable to measure a coronary artery calcium score to guide clinician-patient risk discussion [236].

For purposes of shared clinical decision making, the AHA/ACC categorizes patients according to level of cardiovascular disease risk at 10 years and recommends routine clinician-patient ASCVD risk discussion in relation to the level of risk [24; 236]:

- Low (<5%): Risk discussion should emphasize healthy lifestyle to reduce risk.
- Borderline (5% to <7.5%): If there are risk enhancers present, then risk discussion regarding benefit of moderate-intensity statin therapy.
- Intermediate (7.5% to <20%): If risk estimate plus added risk enhancers favor statin therapy, discussion on benefit of initiating moderate-intensity statin to reduce LDL-C by 30% to 49%.
- High (≥20%): Discussion on benefit of statin therapy to reduce LDL-C by 50% or more combined with adoption of a healthy lifestyle.

A 10-year "intermediate" risk score (10% to 15%) does not automatically mandate a statin, but rather should lead to discussion and shared decision-making between the clinician and the patient [229]. Drug therapy is recommended only in select patients with moderately-high LDL (≥160 mg/dL) or patients with very-high LDL (190 mg/dL).

Two higher-risk patient categories are those with severe hypercholesterolemia (LDL ≥190 mg/dL) and older adults with diabetes. Patients with severe hypercholesterolemia and adults 40 to 75 years of age with diabetes are candidates for immediate statin therapy without further risk assessment. Adults with diabetes should start with a moderate-intensity statin (i.e., one that lowers LDL by 30% to 49%). A high-intensity statin (i.e., one that lowers LDL by ≥50%) may be indicated as the patient accrues multiple risk factors. In all other adults 40 to 75 years of age, the 10-year risk of ASCVD should guide therapeutic decision making. The higher the 10-year risk, the more likely the patient will benefit from evidence-based statin treatment [24].

CLINICAL GUIDELINES FOR THE TREATMENT OF HYPERLIPIDEMIAS

Treatment guidelines for hyperlipidemias were developed by the NCEP-ATP III [230]. These guidelines were partially updated by the 2013 ACC/AHA guideline; however, as discussed, the recommendations provided by the 2018 AHA/ACC guideline and adapted by the 2019 AHA/ACC guideline on primary prevention of CVD will be presented [24; 236]. In 2020, the Department of Veterans Affairs and the Department of Defense (VA/DoD) also published a clinical practice guideline for the management of dyslipidemia [237]. The VA/DoD guideline is designed for the adult population older than 40 years of age and eligible for healthcare in the VA and DoD health systems. Healthcare professionals working within the VA and DoD systems, and others participating in care of patients within the systems, may wish to review the VA/DoD document, as there are differences between these guidelines and the AHA/ACC guidelines, such as the intensity of statin recommended, the risk level thresholds for statin treatment, and the use of adjunctive therapies for primary prevention in patients on statins [238].

Guidelines on management of hyperlipidemia specify four major categories of patients for whom statins may be considered (***Table 9***) [24]:

- Those with clinical ASCVD
- Those with severe hypercholesterolemia (LDL ≥190 mg/dL)
- Those 40 to 75 years of age with diabetes and LDL ≥ 70 mg/dL
- Those 40 to 75 years of age with no diabetes but with LDL ≥ 70 mg/dL and ≥ 7.5% 10-year ASCVD risk

In addition to the patient factors discussed, race and ethnicity inform and influence the estimates of ASCVD risk, treatment intensity, use of lipids, and other issues. For example, when evaluating ASCVD risk, it is useful for the clinician to know that risk in people of South and East Asian origin varies by country of origin. When evaluating lipid issues, it is useful to know that Hispanic/Latina women have a higher prevalence of low HDL compared with Hispanic/Latino men. When evaluating metabolic issues, it is useful to know that there is an increased prevalence of diabetes and hypertension among Black Americans. Country-specific race/ethnicity, along with the patient's socioeconomic status, may affect the estimation of risk by pooled cohort equations [24].

Other at-risk patient groups include those with moderate or severe hypertriglyceridemia, women with gender-specific history (e.g., premature menopause, history of pregnancy-associated disorders), adults with chronic kidney disease, adults with chronic inflammatory disorders and HIV, older adults (≥75 years of age), young adults (20 to 39 years of age), and children and adolescents. The 2018 AHA/ACC guideline provides recommendations and considerations for clinical decision-making for these unique patient populations [24]. Additionally, the guideline continues to emphasize adherence to a heart-healthy lifestyle from adolescence onward; promote assessment of lifetime ASCVD risk for young adults 20 to 40 years of age; and emphasize comprehensive lifestyle improvements to prevent development of metabolic syndrome [231].

Adherence to changes in lifestyle and effects of LDL-lowering medication should be assessed by measuring fasting lipids 4 to 12 weeks after initiation of statin therapy or dose adjustment, and every 3 to 12 months thereafter to assess adherence and safety indicators. Good adherence to an LDL-lowering diet will reduce LDL levels by 10% to 15%. Moderate-intensity statins may reduce LDL levels by another 30% to 40%, and high-intensity statins by ≥ 50%. The intensity of statin therapy will vary according to the patient's age and risk category [24].

The 2022 AHA/ACC/HFSA Guidelines for the management of Heart Failure recommend the use of sodium-glucose cotransporter-2 inhibitors (SGLT2is) in the treatment of heart failure with reduced ejection fraction [241]. Numerous randomized controlled trials have found that patients with diabetes and ASCVD without heart failure have improved survival and reduced hospitalizations when treated with SGLT2is. SGLT2i therapy prevents heart failure hospitalizations in patients with type 2 diabetes and improves outcomes in patients with heart failure with reduced ejection fraction whether or not they also have diabetes [242]. The mechanism of action of SGLT2i on the improvement in heart failure events is still not clearly elucidated, but it seems to be independent of glucose lowering effects. Proposed mechanisms include [242]:

- Promotion of osmotic diuresis and reductions in plasma volume in patients with and without diabetes, therefore reducing cardiac preload
- Improvements in endothelial function and promotion of peripheral vasodilation, therefore reducing cardiac afterload
- Improvements in myocardial metabolism, reduction of arterial stiffness, and interaction with the Na+/H+ exchanger, improving cardiac efficiency

The recommendations in the 2022 AHA/ACC/HFSA guidelines are also in agreement with the Heart Failure Guidelines Update of the Canadian Cardiovascular Society, published in 2021 [243].

CONCLUSION

Cardiovascular diseases are a leading cause of death in developed countries. Although the prevalence of ASCVD in developed countries has increased in the past 40 years, the mortality rate has declined as the result of advances in diagnosis and medical and surgical treatments.

AHA/ACC RECOMMENDATIONS FOR STATIN THERAPY			
Age	**Patient Factors**	**Recommendation**	**Target % LDL**
Patients with ASCVD			
≤75 years	Clinical ASCVD	High-intensity statin (initiate or continue)	≥50%
	Clinical ASCVD and contraindication to high-intensity statin	Moderate-intensity statin (initiate or continue)	30% to 49%
	Clinical ASCVD, at very high risk, being considered for PCKS9 inhibitor therapy	Maximally-tolerated LDL-lowering therapy (with maximally tolerated statin and ezetimibe)	
	Clinical ASCVD, at very high risk, on maximally tolerated LDL-lowering therapy, with LDL ≥70 mg/dL or non-HDL ≥100 mg/dL	It is reasonable to add PCSKP-I following clinician-patient discussion	
	Clinical ASCVD, on maximally tolerated statin therapy, at very high risk, with LDL ≥70 mg/dL	It is reasonable to add ezetimibe	
≥75 years	Clinical ASCVD and evaluated for ASCVD risk reduction, statin adverse effects, drug-drug interactions, patient frailty and preferences	It is reasonable to initiate moderate- or high-intensity statin	30% to 49%
	Currently tolerating high-intensity statin therapy and evaluated for ASCVD risk reduction, statin adverse effects, drug-drug interactions, patient frailty and preferences	It is reasonable to continue high-intensity statin	
	Clinical ASCVD, currently receiving maximally tolerated statin therapy but LDL level remains ≥70 mg/dL	It may be reasonable to add ezetimibe	
	Heart failure and reduced ejection fraction attributable to ischemic heart disease and reasonable life expectancy (3 to 5 years), not on statin therapy due to ASCVD	May consider initiation or moderate-intensity statin therapy	
	Clinical ASCVD, on maximally tolerated statin therapy, at very high risk, with LDL ≥70 mg/dL	It is reasonable to add ezetimibe	
Patients with Severe Hypercholesterolemia			
20 to 75 years	LDL ≥190 mg/dL	Maximally-tolerated statin therapy	≥50%
	LDL ≥190 mg/dL, achieves <50% reduction in LDL while receiving maximally tolerated statin and/or have LDL ≥100 mg/dL	Ezetimibe therapy is reasonable	
	Baseline LDL ≥190 mg/dL, achieves <50% reduction in LDL levels and has fasting triglycerides ≤300 mg/dL while taking maximally tolerated statin and ezetimibe therapy	Consider adding a bile acid sequestrant	
30 to 75 years	Heterozygous FH with LDL ≥100 mg/dL while taking maximally tolerated statin and ezetimibe therapy	Consider adding a PCSK9 inhibitor	≥50%
40 to 75 years	Baseline LDL ≥220 mg/dL, achieves on-treatment LDL ≥130 mg/dL while receiving maximally tolerated statin and ezetimibe therapy	Consider adding a PCSK9 inhibitor	≥50%

Table 9 continues on next page.

AHA/ACC RECOMMENDATIONS FOR STATIN THERAPY			
Age	**Patient Factors**	**Recommendation**	**Target % LDL**
Patients with Diabetes			
40 to 75 years	Diabetes	Moderate-intensity statin, regardless of estimated 10-year ASCVD risk	–
	Diabetes and LDL 70–189 mg/dL	Reasonable to assess 10-year risk of first ASCVD event using race-, sex-specific pooled cohort equations	–
	Diabetes with multiple ASCVD risk factors	Reasonable to prescribe high-intensity statin	≥50%
≥75 years	Diabetes and on statin therapy	Reasonable to continue statin therapy	
	Diabetes and 10-year ASCVD risk ≥20%	May be reasonable to add ezetimibe to maximally tolerated statin	≥50%
>75 years	Diabetes	May be reasonable to initiate statin therapy after clinician-patient risk discussion	–
20 to 39 years	Diabetes with specific risk enhancers[a]	May be reasonable to initiate statin therapy	–
Patients with No Diabetes But Other Risk Factors			
40 to 75 years	LDL ≥70 mg/dL and 10-year ASCVD risk ≥7.5%	Moderate-intensity statin, if favored by clinician-patient risk discussion	–
[a]Diabetes of long duration (≥10 years type 2, ≥20 years type 1), albuminuria, eGFR <60 mL/min/1.73 m^2, retinopathy, neuropathy, ankle-brachial index <0.9			
Source: [24]			*Table 9*

The complex interaction between modifiable, non-modifiable, and risk-enhancing risk factors underlies the etiology of ASCVD. It is now well established that hyperlipidemias, and high concentrations of LDL in particular, are implicated in the etiology of atherosclerosis and increased incidence of ASCVD such as coronary artery disease, peripheral vascular disease, and ischemic cerebrovascular disease. Hyperlipidemias are also associated with primary hypertension and metabolic syndrome. As a result, prevention, early diagnosis, and appropriate clinical management of hyperlipidemias have become a public health priority.

Effective lipid management slows the progression of atherosclerosis and lowers morbidity and mortality associated with ASCVD. This requires not only a change in general perceptions but also a multidisciplinary approach to prevention that involves all members of the healthcare team, including physicians, nurses, pharmacists, dietitians, counselors, and physiotherapists.

The evidence-based guidelines for the assessment of cardiovascular risk, treatment goals, lifestyle changes, and pharmacotherapy developed by the AHA/ACC should be followed as the gold standard in clinical practice [24; 95; 115; 120; 227]. The primary target in the treatment of hyperlipidemias is to lower LDL; the secondary targets are treating high triglycerides, low HDL, and metabolic syndrome. A variety of lipid-lowering drugs with a favorable risk-benefit profile, in conjunction with implementation of lifestyle changes, is available to meet these goals.

A better understanding of the molecular elements and physiology of the exogenous and endogenous lipid pathways has played a fundamental role in the development of the most potent lipid-lowering drugs. Scientific advances have led to the development of a newer generation of drugs, now undergoing several stages of clinical evaluation, with the potential to improve on existing drugs' risk-benefit profiles. The important role played by the implementation of lifestyle changes, including a balanced diet, in achieving a healthy lipid profile and decreasing the incidence of ASCVD cannot be overstated and should be an integral part of disease management.

COURSE TEST - #90844 HYPERLIPIDEMIAS AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

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.

This 10 Hour activity must be completed by July 31, 2025.

1. Atherosclerotic cardiovascular disease (ASCVD) accounts for approximately what percentage of deaths in the United States?
- A) *10%*
- B) *26%*
- C) *31%*
- D) *55%*

2. Approximately what percentage of Americans 20 years of age or older have total blood cholesterol levels in excess of 240 mg/dL?
- A) *5%*
- B) *8%*
- C) *11.5%*
- D) *15%*

3. Which of these statements regarding atherosclerosis is TRUE?
- A) *Atherosclerosis is initiated during middle-age.*
- B) *Atherosclerosis is a process that targets small sized arteries.*
- C) *Atherosclerosis is rapidly accelerated by genetic and environmental factors.*
- D) *All of the above*

4. All of the following are progressive stages of atherosclerosis, EXCEPT:
- A) *plaque formation.*
- B) *plaque disruption.*
- C) *fatty streak formation.*
- D) *high-density lipoprotein.*

5. Which of the following is NOT considered a biomarker for ASCVD?
- A) *Age*
- B) *Lipoprotein(a)*
- C) *C-reactive protein*
- D) *Hyperhomocysteinemia*

6. The role of lipoprotein(a) in atherogenesis relates to a variety of mechanisms, EXCEPT:
- A) *low affinity for the LDL-receptor.*
- B) *decelerated smooth cell proliferation.*
- C) *enhanced capacity to traverse the arterial endothelium.*
- D) *inhibition of fibrinolysis by preventing the transformation of plasminogen to plasmin.*

7. Dietary lipids account for what percentage of calories in western diets?
- A) *10% to 20%*
- B) *20% to 30%*
- C) *30% to 40%*
- D) *40% to 50%*

8. What is the main site of lipid transformation and absorption?
- A) *Mouth*
- B) *Stomach*
- C) *Small intestine*
- D) *Large intestine*

9. Which of the following statements regarding chylomicrons is FALSE?
- A) *Chylomicrons are only synthesized in the intestine.*
- B) *Chylomicrons are composed mainly of triglycerides.*
- C) *Chylomicrons are large lipoproteins very rich in lipids.*
- D) *Chylomicrons have the highest protein content of any lipoprotein.*

10. Increased LDL levels can result from
- A) *a deficiency of estrogens.*
- B) *a deficiency of thyroid hormones.*
- C) *genetic mutations of either the LDL receptor or Apo B-100.*
- D) *All of the above*

11. Which of the following statements regarding HDLs is TRUE?
- A) *HDLs are the largest lipoproteins.*
- B) *The protein content of HDLs is 33%.*
- C) *HDL removes cholesterol from the periphery and transports it to the kidneys.*
- D) *The two most important subclasses of HDL express either Apo A-II alone or both Apo A-I and A-II.*

12. Research has shown that moderate-to-high HDL levels may help to prevent ASCVD. The main goal for patients with hyperlipidemias should be to
- A) *increase HDL levels.*
- B) *decrease LDL levels.*
- C) *increase triglyceride levels.*
- D) *All of the above*

13. As primary hyperlipidemia progresses, the following signs and symptoms develop, EXCEPT:
- A) *obesity.*
- B) *lipemic plasma.*
- C) *eruptive xanthomas.*
- D) *severe hypertriglyceridemia.*

14. With an incidence greater than 25% in the United States, the most common form of hyperlipidemia is
- A) *atherogenic dyslipidemia.*
- B) *familial hypertriglyceridemia.*
- C) *familial hypercholesterolemia.*
- D) *polygenic hypercholesterolemia (or nonfamilial hypercholesterolemia).*

15. Secondary hyperlipidemias can be precipitated by the use of certain medication treatments. These treatments include estrogen therapy, atypical antipsychotics, corticosteroids, and
- A) *statins.*
- B) *fibrates.*
- C) *thiazides.*
- D) *antioxidants.*

16. Secondary hyperlipidemia with elevated cholesterol is the main dyslipidemia in patients with
- A) *obesity.*
- B) *alcohol abuse.*
- C) *chronic renal failure.*
- D) *hormone replacement therapy.*

17. The primary goal of lipid therapy in high-risk patients is to reduce LDL cholesterol by
- A) *10%.*
- B) *25%.*
- C) *40%.*
- D) *50% or more.*

18. The 2018 and 2019 AHA/ACC guideline recommendations for a heart-healthy dietary pattern include all of the following, EXCEPT:
- A) *Low-fat dairy products*
- B) *Increased calories from trans fats*
- C) *Fruits, vegetables, and whole grains*
- D) *No more than 5% to 6% of calories from saturated fats*

19. Which of the following statements regarding lipid management through lifestyle change is TRUE?
- A) *Lipid lowering goals can usually be achieved on one's own.*
- B) *Lipid lowering through diet and exercise will not reduce the risk for ASCVD and mortality.*
- C) *Successful lipid control usually requires instruction by a dietitian or other knowledgeable healthcare professional.*
- D) *In patients with high cardiovascular risk and/or very high LDL, medication therapy should be initiated if lifestyle changes are not effective within a two- to three- month period.*

20. Bile acids are the source of what percentage of cholesterol in the intestine?
- A) *25%*
- B) *50%*
- C) *75%*
- D) *100%*

21. The cholesterol absorption inhibitor ezetimibe can increase the efficacy of what other treatment by 25%?
- A) *Statins*
- B) *Niacin*
- C) *Fish oil*
- D) *Fibrates*

22. Of the following, which statin is among the most effective in its class?
- A) *Lovastatin*
- B) *Fluvastatin*
- C) *Pravastatin*
- D) *Simvastatin*

Test questions continue on next page ➜

23. In addition to lowering lipid levels, statins are thought to have all of the following pleiotropic effects, EXCEPT:

A) neuroprotection.
B) modulation of endothelial function.
C) an increase in vascular inflammation.
D) immunomodulation by inhibition of major histocompatibility complex II expression.

24. To achieve optimum lipid control in patients with dyslipidemia, the initial dosage of any statin should be based on which factor?

A) Age
B) Cost
C) Body mass
D) LDL percentage reduction

25. Compared to statin monotherapy, bile acid-binding resin/statin combinations decrease LDL levels by what percentage?

A) 8% to 10%
B) 18% to 20%
C) 20% to 30%
D) 40% to 50%

26. Niacin, or nicotinic acid, is also known as what vitamin?

A) Vitamin B3
B) Vitamin D2
C) Vitamin E2
D) Vitamin B12

27. Which of the following statements regarding niacin is TRUE?

A) It has high cost.
B) It is no longer recommended, except in specific clinical situations.
C) Randomized controlled trials support is use as an add-on to statin therapy.
D) It has been shown to reduce ASCVD outcomes beyond that achieved with statins.

28. Omega-3 fatty acids are abundant in what dietary sources?

A) Walnuts
B) Fatty fish
C) Canola oil
D) All of the above

29. Because they can be synthesized in the body, which of these fatty acids are considered non-essential?

A) Omega-3 fatty acids
B) Omega-6 fatty acids
C) Omega-9 fatty acids
D) None of the above

30. According to the AHA/ACC, for patients 75 years of age or younger with clinical ASCVD on high-intensity therapy, the target percentage LDL reduction should be

A) 10%.
B) 20%.
C) 40%.
D) 50% or greater.

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