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Antibiotics Review

Audience
This course is designed for healthcare providers who prescribe and administer antibiotics to patients, including pharmacists, physicians, physician assistants, pharmacy technicians, nurses, nurse practitioners, and surgical technologists and assistants.

Course Objective
The purpose of this course is to provide a review of the major classes of antibiotics and their characteristics as well as an overview of selected individual agents within each class that are most useful for today's clinical practitioner.

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

1. Describe the general characteristics and mode of action of antibiotics commonly in use.
2. Employ best practice principles for limiting the emergence and transmission of antimicrobial-resistant strains within the healthcare environment, including in surgical practices.
3. Discuss the mechanism of action, pharmacokinetics, and spectrum of activity of natural and extended-spectrum penicillins.
4. Select the most appropriate, cost-effective cephalosporin based on "generational" characteristics and spectrum of activity.
5. Describe the role of carbapenems and monobactams.
6. Discuss the characteristics, expected toxicities, and indications for the use of aminoglycosides, macrolides, and sulfonamides.
7. Outline the mechanism of action, pharmacokinetics, and advantages inherent to quinolones and the tetracyclines.

Faculty
Donna Coffman, MD, attended medical school at the University of Louisville and completed her residency in Family Practice at St. John's Mercy Medical Center in St. Louis, Missouri. She is board-certified in Family Medicine and currently on staff at John Cochran VAMC in St. Louis.

Faculty Disclosure
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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

The number of antibiotic agents available is remarkable, and new agents are added regularly. This course is intended as an overview of the general characteristics of the major antibiotic classes, emphasizing mechanism of action, pharmacokinetics, and potential toxicities, with a brief discussion of the individual member agents and their clinical indications. The purpose of this course is to enlarge clinical perspective and enhance the understanding and confidence required for the selection of appropriate therapy of bacterial infections. The goal is to improve efficacy and safety while limiting the risk for selection and transmission of antimicrobial-resistant pathogens.

Given the large array of available antimicrobial agents, the scope of this course is confined to the eight major classes of antibiotics commonly employed for acute bacterial infection: the penicillins, cephalosporins, carbapenems, aminoglycosides, quinolones, macrolides, sulfonamides, and tetracyclines. A brief discussion of vancomycin, daptomycin, and newer glycopeptide analogues available for treatment of multi-resistant *Staphylococcus aureus* (MRSA) and enterococcal species is included.

For the purposes of the course, it is impractical to list or describe all the possible adverse effects, recommended uses, and off-label uses of the antibiotics discussed. Before using any antimicrobial, it is important to review the manufacturer's package insert and dosing recommendations for the drug.

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GENERAL CHARACTERISTICS OF ANTIBIOTICS

There are some characteristics that all antibiotics share. All antibiotics can elicit allergic responses, although some are more allergenic than others. Allergic reactions can range from mild, annoying rashes to life-threatening reactions such as anaphylaxis and the Stevens-Johnson syndrome. In some cases, there is a cross-sensitivity between agents in different classes. In addition, all antibiotics exert some impact on normal body flora as well as pathogens, in some cases leading to the emergence of *Candida* species and pathogenic bacteria such as *Clostridioides difficile*. Overgrowth of *C. difficile* within intestinal flora is often a serious complication of antimicrobial therapy that can produce symptoms ranging from mild diarrhea to severe, life-threatening pseudomembranous colitis [1]. Most cases resolve with supportive care and discontinuation of the offending antibiotic, but many require treatment. Furthermore, *C. difficile* colitis can develop days or weeks after the primary antimicrobial has been discontinued. A high degree of suspicion and judicious use of laboratory testing are the keys to recognizing and managing these complications.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America, the infusion of bezlotoxumab should be performed while a patient is receiving standard-of-care antibiotics and has been shown to be effective in preventing recurrent *C. difficile* infection if administered at any time before ending antibacterial treatment

(https://academic.oup.com/cid/article/73/5/e1029/6298219. Last accessed January 11, 2024.)

Strength of Recommendation: Expert Opinion/Consensus Statement

ANTIBIOTIC RESISTANCE

Repeated exposure to an antibiotic may lead to the emergence of selective subpopulations of the same or related bacteria now resistant to the therapeutic agent. The Centers for Disease Control and Prevention (CDC) note that approximately 2.8 million people become infected with bacteria that are resistant to antibiotics, and approximately 35,000 people die annually because of these infections [2]. When *C. difficile* colitis, not typically resistant but associated with antimicrobial use, is added to these, the U.S. toll of all threats exceeds 3 million infections and 48,000 deaths [2]. Mechanisms of microbial resistance include altered cellular permeability (leading to greatly diminished intracellular concentration of the drug), increased efflux of the antibiotic from the cell, and elaboration of deactivating enzymes that alter the antibiotic's interaction at binding sites within the cell wall or cytoplasm [3].

Decreased cell membrane permeability is an important mechanism of bacterial resistance to beta-lactams, quinolones, and vancomycin. Microbial resistance to tetracyclines and quinolones is often mediated by increased efflux of the antibiotic from the cell. Enzymatic deactivation by beta-lactamases is the common mechanism of resistance to penicillins and cephalosporins. Resistance to aminoglycosides may result from altered cytoplasmic membrane transport (influx) or from intracellular enzymes (e.g., phosphotransferases and acetyltransferases) that deactivate the drug.

There are various mechanisms by which the interaction of an antibiotic with its binding site may be altered or bypassed, resulting in loss of antimicrobial activity. One such example, affecting the target site for quinolone activity, is an acquired structural alteration of deoxyribonucleic acid (DNA) gyrase, an enzyme essential for bacterial DNA synthesis. As a result, quinolones are no longer able to bind to the enzyme and the drug loses its antimicrobial effect. Another example is the methylation of ribosomal ribonucleic acid (rRNA) that prevents the binding of macrolides. The effectiveness of trimethoprim/sulfamethoxazole, which acts through disruption of folate synthesis by the cell, may become diminished by the adaptive ability of some bacteria to utilize an alternate metabolic pathway, thereby avoiding the effects of trimethoprim [4].

These resistance mechanisms may be acquired through mutations in the genes that encode for the target or affected transport proteins. As the bacterial cells without the adaptive mutations succumb to the action of the antibiotic, the subpopulation that has the adaptive mutation continues to replicate, replacing the original population with a resistant one.

Bacterial resistance can be transferred from one bacterium to another, or from one bacterial species to related group, by means of plasmids or transposons that gain entry to the cell. These agents are small segments of DNA that are readily exchanged between bacteria. A plasmid that contains a gene for an adaptive mutation can be shared with many nearby bacteria, which may or may not be the same species. In this manner, resistance can quickly spread from species to species [5].

Many strategies have been used to circumvent the multiple mechanisms of resistance encountered in bacteria. Among these are addition of beta-lactamase inhibitors to extended-spectrum penicillins, alteration of cephalosporin side chains to produce new generations of the drug with broader activity, and combining drugs to enhance the antimicrobial effect (e.g., sulfamethoxazole with trimethoprim). In 2021, in response to perceived overuse of antibiotics, the American College of Physicians recommended limiting antibiotic courses to five to seven days for the some of the most common bacterial infections, including durations of antibiotic therapy in patients

with common bacterial infections, such as acute bronchitis, community-acquired pneumonia, urinary tract infection, and cellulitis [172].

EVIDENCE-BASED PRACTICE RECOMMENDATION

A meta-analysis published by the *Cochrane Database of Systematic Reviews* found high-certainty evidence that any professional or structural interventions are effective in increasing compliance with antibiotic policy and reducing duration of antibiotic treatment in the hospital setting.

(https://www.cochrane.org/CD003543/EPOC_improving-how-physicians-working-hospital-settings-prescribe-antibiotics. Last accessed January 11, 2024.)

Level of Evidence: Meta-analysis

In addition, new categories of antibiotics are being created to stay ahead of the rapid evolution of bacterial resistance. Linezolid and tedizolid, the only two FDA-approved drugs in the oxazolidinone category, are examples of this, with linezolid being the first of the two to be developed. Oxazolidinones are a unique category of drugs that prevent formation of the 70S protein synthesis complex in bacteria and may be useful in the treatment of vancomycin-resistant enterococci and MRSA [6; 7]. Nonetheless, development of resistance in bacteria is relentless.

Considering the efficient means by which bacteria develop resistance, clinicians should avoid, where possible, practice patterns that contribute to the process. In 2002, the CDC issued a position paper outlining recommendations for minimizing nosocomial infection and the emergence of resistant organisms [8]. In this paper, the CDC recommended a multistep approach that included: preventing infection (by paying careful attention to the proper use of invasive medical devices); tailoring medical treatment to fit the infection (by avoiding broad-spectrum antibiotics and prolonged treatment when possible); and preventing the transmission of resistant bacteria between patients (by emphasizing hand washing and implementing hospital infection control programs) [8]. Since issuance of the CDC's position paper, the agency has taken many additional steps and implemented coordinated, strategic action plans to change the course of antibiotic resistance. This includes publication of *The National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB), 2020–2025* [9]. The CARB builds on the first National Action Plan, released in 2015, and prioritizes infection prevention and control to slow the spread of resistant infections and reduce the need for antibiotic use. The CARB also integrates a "one health" approach, which recognizes the relationships between the health of humans, animals, plants, and the environment [9]. It has also been hypothesized that the response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and associated COVID-19 illness might increase use of antibiotics and other antimicrobial medicines (both appropriate and inappropriate) to address primary or secondary infections, with the potential to further accelerate the emergence of antibiotic resistance despite the rate of the development of new antibiotics [9].

In 2022, the CARB Task Force issued a Year 5 Progress Report on combating antimicrobial-resistant bacteria, summarizing accomplishments achieved between 2015 and 2020. This report showed that substantial progress had been achieved for the following targeted bacteria: health care-associated *C. difficile* infection decreased by 36%; hospital-onset multidrug-resistant *Pseudomonas aeruginosa* decreased by 41%; and hospital-onset MRSA bloodstream infections decreased approximately 31.5% [173].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

Obtaining a detailed patient history is a vital aspect of the appropriate prescription of antibiotics, particularly in empirical treatment. Furthermore, communication with patients regarding treatment regimens and compliance depends on clear communication between the patient and clinician. 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. The interpreter should be considered an active agent in the diagnosis and/or treatment processes, negotiating between two cultures and assisting in promoting culturally competent communication and practice [10].

PENICILLINS

Alexander Fleming discovered penicillin in 1928. After observing that *Penicillium* colonies inhibited the growth of staphylococci on agar plates, Fleming made an extract from the mold and proved that it inhibited bacterial growth. Penicillin became available for general use in the 1940s [11].

MECHANISM OF ACTION

Penicillin is bactericidal, killing susceptible bacteria by interrupting cell wall synthesis. The drug exerts its effect by preventing cross-binding of the peptidoglycan polymers necessary for cell wall formation and by binding with carboxypeptidases, endopeptidases, and transpeptidase ("penicillin-binding proteins" [PBPs]) that participate in cell wall synthesis [12]. Although the exact mechanisms involved are not known, the result is that the cell wall is structurally weakened and lyses, leading to cell death.

The basic form of penicillin is structured around the beta-lactam ring (a thiazolidine ring) and can be altered by substituting side chains. By doing so, the antimicrobial spectrum, absorption characteristics, and resistance to beta-lactamase deactivation can be favorably modified.

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Bacterial resistance to penicillins may take different forms. The most significant is the bacterial production of beta-lactamases, which can destroy the beta-lactam ring by means of hydrolysis, effectively preventing antimicrobial activity by the agent [13]. In addition, some bacteria are able to prevent binding to the PBPs by various means, including altered binding sites for the penicillins [14].

Various strategies have been employed to circumvent these microbial adaptations. Altering the structure of the penicillin molecule to produce agents that are more resistant to the hydrolysis from the beta-lactamases has resulted in the development of the extended-spectrum penicillins.

Another strategy has been to combine penicillins with other agents that block bacterial beta-lactamases [6]. Examples include amoxicillin plus clavulanic acid, ampicillin plus sulbactam, piperacillin plus tazobactam, and ticarcillin plus clavulanic acid. Clavulanic acid is produced by *Streptomyces clavuligerus*. Sulbactam and tazobactam are derived from the basic penicillin ring. These agents have little intrinsic antimicrobial activity, but they bind irreversibly to many beta-lactamases, preventing hydrolytic activity against the beta-lactam ring.

PHARMACOKINETICS

Penicillins can be separated into groups based on their pharmacokinetics and spectrum of antibacterial activity. These groups are the natural penicillins, the aminopenicillins, the penicillinase-resistant penicillins, and the antipseudomonal penicillins [15].

The Natural Penicillins

The natural penicillins include various penicillin G preparations and penicillin V potassium. Penicillin G is very unstable in stomach acid and must be given parenterally. Penicillin V potassium is more acid-stable and is the appropriate form for oral administration.

The natural penicillins are active against gram-positive organisms such as streptococci, *Enterococcus faecalis*, and *Listeria monocytogenes*. However, most *S. aureus* isolates are now resistant. The natural penicillins are also active against anaerobic species, such as *Bacteroides* species and *Fusobacterium* species. At serum levels achieved by parenteral administration, the natural penicillins are effective against some gram-negative bacteria, such as *Escherichia coli*, *H. influenzae*, *Neisseria gonorrhoeae*, and *Treponema pallidum*. For the treatment of moderate-to-severe infections in which resistant organisms are considered a possibility, reliance upon penicillin alone should be avoided unless the identity and sensitivity of the infecting organism have been confirmed. Labeled uses include treatments for infections of the upper and lower respiratory tract, throat, skin, and genitourinary tract and prophylaxis of recurrent rheumatic fever and pneumococcal infections [6].

The Aminopenicillins

The aminopenicillins have about the same activity as the natural penicillins against susceptible gram-positive organisms, plus improved coverage of selected gram-negative bacilli, including *Enterobacteriaceae*. Amoxicillin/clavulanic acid and ampicillin/sulbactam have better coverage against *H. influenzae* and *Klebsiella* species than the natural penicillins and the aminopenicillins alone.

The aminopenicillins include ampicillin and amoxicillin. Ampicillin can be given parenterally or orally. These agents are useful for the management of sinusitis/bronchitis, endocarditis, meningitis, susceptible urinary tract infection, and salmonellosis [6]. Amoxicillin is the best absorbed of the oral penicillins. It is acid-stable and its absorption, unlike ampicillin, is not much affected by food. Improved absorption is also thought to provide an advantage over ampicillin in reducing the risk of antibiotic-associated diarrhea. Labeled uses include endocarditis prophylaxis and as a component of a multidrug *H. pylori* eradication regimen [6].

The Penicillinase-Resistant Penicillins

The penicillinase-resistant penicillins were developed in response to the emergence of penicillinase-producing *S. aureus*. These penicillins are resistant to hydrolysis by the lactamase produced by the staphylococci, and they include nafcillin and oxacillin, which are parenteral formulations, and dicloxacillin, which is given orally. Methicillin and cloxacillin are no longer available in the United States [6].

Although penicillinase-resistant penicillins have the same spectrum of activity against many of the same gram-positive pathogens as the natural penicillins, they lack significant activity against gram-negative or anaerobic organisms. They are, however, notable for their usefulness against penicillin-resistant (methicillin-sensitive) *Staphylococcus* species.

The Antipseudomonal Penicillins

The antipseudomonal penicillins are often also referred to as extended-spectrum penicillins; these include ticarcillin and piperacillin (both of which are parenteral). Mezlocillin, which was also parenteral, and carbenicillin, which could be administered orally, are no longer available in the United States [6; 17].

The extended-spectrum penicillins retain their activity against gram-positive bacteria and anaerobic gram-negative pathogens such as *Bacteroides* fragilis. However, these agents were developed because of their excellent activity against *Pseudomonas aeruginosa* and other multidrug-resistant gram-negative pathogens, including *Klebsiella* species and *Serratia* species. The antipseudomonal penicillins are effective for treatment of *H. influenzae* as well.

THE PENICILLINS					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Natural Penicillins					
Penicillin G benzathine	1.2–2.4 MU	50,000 U/kg in one dose Max: 2.4 MU divided between 2 injection sites	IM	Rash, GI upset	Indicated for syphilis and group A strep infections. Note: Do not administer IV (except parenteral/aqueous preparation) or IM near nerve or artery. Cardiopulmonary arrest and death have occurred from accidental IV administration.
Penicillin G benzathine or penicillin G procaine	2.4 MU in one dose	<14 kg: O.6 MU 14 to 27 kg: 1.2 MU in one dose	IM	Rash, GI upset	
Penicillin G (parenteral/ aqueous)	2–30 MU per day	100,000–400,000 U/ kg/day in divided doses every 4 to 6 hours Max: 24 MU/day	IM, IV	Rash, GI upset	
Penicillin V potassium	125–500 mg every 6 to 8 hours	Pneumonia (off label): 50–75 mg/kg/day in 3 to 4 divided doses Pharyngitis: 250 mg 2 to 3 times per day	PO	Rash, GI upset	--
Aminopenicillins					
Amoxicillin	250–500 mg every 8 hrs, or 500–875 mg twice daily	Manufacturer recommendation: >3 months and <40 kg: 20–100 mg/ kg/day in divided doses every 8 to 12 hrs ≤3 months: 20–30 mg/kg/day divided every 12 hrs AAP recommendation: All infants and children <40 kg: 25–50 mg/kg/day in divided doses every 8 hrs	PO	Rash, diarrhea	Not to be confused with amoxicillin/clavulanate ES formulation. Extended-release tablet 775 mg once daily for adults and children ≥12 years of age
Amoxicillin/ clavulanate	250–500 mg every 8 hrs, or 875 mg every 12 hrs	15–40 mg/kg/day divided every 8 hrs, or 25–45 mg/kg/day divided every 12 hrs Max: 4g/day <3 mos: 30 mg/kg/day every 12 hrs (125 mg/5 mL suspension only)	PO	Rash, diarrhea	Dosing for amoxicillin/ clavulanate is based on the amoxicillin component; the ES formulation of amoxicillin/clavulanate is not interchangeable with the regular suspension and requires product specific dosing.
Ampicillin	250–500 mg every 6 hrs	PO: 50–100 mg/kg/ day in 4 divided doses Max: 2–4 g/day IV, IM: 25–200 mg/ kg/day every 3 to 4 hrs Max: 12 g/day	PO, IV, IM	Rash, GI symptoms (very common)	The IV form can be given in divided doses or in a continuous infusion.

Table 1 continues on next page.

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THE PENICILLINS *(Continued)*					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Ampicillin/ sulbactam	1.5–3 g every 6 hrs IV	≥1 year: IV: 100–400 mg/kg/day every 6 hrs Max: 8 g/day	IV, IM	Rash, diarrhea, local pain at injection or infusion site (very common with IM use)	Dosing for ampicillin/ sulbactam is based on the ampicillin component.
Penicillinase-Resistant Penicillins					
Dicloxacillin	125–500 mg every 6 hrs	<40 kg: 12.5–100 mg/kg/day in 4 doses divided every 6 hrs >40 kg: 125–250 mg every 6 hrs	PO	Rash, diarrhea	Use with caution in neonates, as elimination of drug is slow.
Nafcillin	IV: 0.5–2 g every 4 to 6 hrs IM: 0.5 g every 4 to 6 hrs	Neonates: 50 mg/kg/ day in 4 divided doses Children: IV: 50–200 mg/kg/day in 4 divided doses IM: 25 mg/kg every 12 hrs	IV, IM	Phlebitis at IV site, neutropenia, rash	Tissue necrosis can occur with IV extravasation.
Oxacillin	0.25–2 g every 4 to 6 hrs	<40 kg: 50–100 mg/ kg/day in divided doses every 6 hrs >40 kg: 250–1,000 mg every 4 to 6 hrs	IV, IM	Phlebitis at IV site, hepatitis, rash	Drug-induced hepatitis is usually reversible if drug is discontinued. Neonatal dosing may require the use of alternate container system/ dosage forms. May contain a significant amount of sodium.
Antipseudomonal Penicillins					
Piperacillin	IV, IM: 3–4 g every 4 to 6 hrs Max: 24 g/day	Neonates: IV, IM: 100 mg/kg every 12 hrs Infants/children: IV, IM: 200–300 mg/kg/day divided every 4 to 6 hrs	IV, IM	Rash, GI upset, phlebitis at infusion site	—
Piperacillin/ tazobactam	IV: 3.375–4.5 every 6 to 8 hrs Max: 18 g/day	Infants 2 to 9 months: 80 mg piperacillin/kg/ dose every 8 hrs Infants and children >9 months: 100 mg piperacillin/kg/dose	IV	Rash, GI upset	Dosing for adults and pediatrics based on traditional infusion method (IV infusion over 30 minutes). Dosage in pediatric patients based on piperacillin component. Pediatric dose is mg/kg/dose, not mg/kg/day.
Ticarcillin or ticarcillin/ clavulanate potassium	<60 kg: 200–300 mg/kg/day divided every 4 to 6 hrs >60 kg: 3.1 g every 4 to 6 hrs Max: 18 g/day	Use adult dosing by weight	IV	Rash, GI upset	Potential warfarin interaction. Ticarcillin/clavulanate doses are based on the ticarcillin component.

Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications.
AAP = American Academy of Pediatrics; MU = million units; ES = extra strength.

Source: [6; 16] *Table 1*

The Addition of Beta-Lactamase Inhibitors

The addition of clavulanic acid, sulbactam, or tazobactam increases the spectrum of activity of the penicillin derivative with which they are combined. They are generally active against the beta-lactamases produced by *H. influenzae*, *Moraxella catarrhalis*, and *S. aureus*. However, their activity is variable against some of the gram-negative bacteria, such as some species of *Pseudomonas*, *Enterobacter*, *E. coli*, *Klebsiella*, and *Serratia*, due to resistance to these beta-lactamase inhibitors [18].

ABSORPTION/ELIMINATION

While most penicillins can be absorbed via the oral route, the bioavailability varies considerably, and food may interfere with absorption. Penicillin V, amoxicillin, ampicillin, and dicloxacillin can be given orally; the remaining penicillins are either too unstable in the acidic environment of the stomach or must be given intravenously in order to achieve sustained therapeutic levels. Amoxicillin is the best absorbed of the oral penicillins and the least affected by a recent meal.

Following oral administration and GI absorption, these agents are widely distributed throughout the body. Therapeutic concentrations of penicillins are readily achieved in tissues and secretions (e.g., joint fluid, pleural fluid, pericardial fluid, and bile). Low concentrations are found in prostatic secretions, brain tissue, intraocular fluid, and phagocytes. Cerebrospinal fluid (CSF) concentrations vary but are less than 1% of serum concentration when the meninges are normal. When the meninges are inflamed, CSF concentrations may rise to 5% and can be increased by co-administration of probenecid (500 mg 4 times daily) [6; 19]. Concentration in urine is high due to renal clearance mechanisms.

Penicillins are excreted in the kidney by means of glomerular filtration and renal tubular secretion. Probenecid markedly reduces the tubular secretion of the penicillins and decreases the apparent volume of distribution, resulting in higher serum levels. All the penicillins are excreted to some degree in the bile, but biliary excretion is most important for antipseudomonal penicillins and nafcillin [20].

In patients with mild renal insufficiency, dosage adjustment is not needed, except with the use of ticarcillin [21]. If the creatinine clearance is less than 50 mL/min, then dosage adjustments of parenteral penicillins should be made to avoid excess serum levels. Nafcillin undergoes extensive hepatic metabolism, and the dosage must be adjusted for severe renal and hepatic insufficiency.

SIDE EFFECTS/TOXICITY

These drugs are usually well tolerated. However, gastrointestinal (GI) disturbances may occur with all oral penicillins.

Allergy to any of the penicillins is the only absolute contraindication to use of a penicillin agent. However, studies have found that penicillin allergy is less common than previously thought [22; 23; 24; 25]. Traditionally, allergic reactions were believed to occur in up to 10% of patients; however, more recent studies have found the rate to be much lower. While penicillin-induced anaphylaxis death rate estimates are similar to previous statistics (i.e., approximately 0.002% among the general population), the percentage of individuals with a true penicillin allergy as defined by immunoglobulin E (IgE)-mediated reaction is generally less than 10%, with some studies showing a true penicillin allergy rate of only 0.7% [22; 23; 24; 26]. It is also important to note that approximately 90% of patients previously diagnosed with a penicillin allergy will show no reactivity if not exposed to the antibiotic for 10 years or more, due to the absence of a true allergy or loss of allergy over time [22; 24; 25]. Allergy skin testing is the most reliable way to determine true penicillin allergy and may allow for previously avoided antibiotics to be used as indicated.

Reactions commonly misdiagnosed as true allergic responses vary and can include a mild rash (the most common) and urticaria. Rarely, serum sickness, exfoliative dermatitis, and Stevens-Johnson syndrome may develop [6; 20]. These responses were originally thought to develop in response to the beta-lactam ring and its derivatives and, therefore, there is a common misperception that penicillins are cross-reactive with other antibiotics with the same beta-lactam structure (e.g., cephalosporins) [6]. However, the major determinant in the immunologic reaction is now recognized to be the similarity in the side chain of first-generation cephalosporins and penicillins (not the beta-lactam structure), with the reaction nearing 0% in third-generation cephalosporins [22; 23; 24].

Rarely, penicillins may cause hematologic reactions with neutropenia due to reversible bone marrow suppression. Abnormal platelet aggregation may occur, particularly with ticarcillin [27]. Other rare reactions include hepatitis, seizures, interstitial nephritis, and hypokalemia due to local effects in the renal tubules.

DRUG INTERACTIONS

The penicillins should not be given concurrently with tetracycline or other bacteriostatic agents. Penicillin works in cells that are actively synthesizing cell wall components, and if metabolism is prevented, then the activity of penicillin is diminished. The antipseudomonal penicillins also may affect warfarin metabolism. Therefore, the prothrombin time, using the international normalized ratio (INR), should be monitored [6; 28].

SPECIAL POPULATIONS

The penicillins are pregnancy category B, indicating no adverse events noted in animal studies [6; 29]. These agents are secreted in breast milk, and breastfeeding should be avoided if the infant is allergic to any of the penicillins [30]. Use while breastfeeding may cause modifications of normal intestinal flora and allergic sensitization in the infant [6].

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CEPHALOSPORINS

Giuseppe Brotzu discovered the first cephalosporin in 1948, observing that the fungus *Cephalosporium acremonium* produced a substance that inhibited the growth of *S. aureus* and other bacteria. The initial substance was identified and modified to create the cephalosporins that are now used. The cephamycins were created by adding a methoxy group on the beta-lactam ring of the original compound, based on the structure of cefoxitin, produced by *Streptomyces lactamdurans*. By altering the chemical groups substituted on the basic molecule, greater antimicrobial activity and longer half-lives have been obtained [31].

MECHANISM OF ACTION

Like penicillins, the cephalosporins are beta-lactams in which the beta-lactam ring is joined to a dihydrothiazine ring. Their antimicrobial effect is based on the same mechanism of action as that for the penicillins. The cephalosporins inhibit bacterial cell wall synthesis by blocking the transpeptidases and other PBPs involved in the synthesis and cross-linking of peptidoglycan [32; 33].

Because each bacterial species has a unique chemical structure in its cell wall, the cephalosporins may have different mechanisms of action by which they inhibit cell wall synthesis.

As with penicillins, resistance to cephalosporins results from mutations in the penicillin-binding proteins (preventing the cephalosporins from binding to them) and from the production of extended-spectrum beta-lactamases that deactivate the drug [34]. An additional source of resistance in gram-negative bacteria is alteration in the cell-membrane porins that normally allow passage of the cephalosporins into the cell [35].

Of these mechanisms, the production of beta-lactamase is the most clinically significant. This form of resistance may occur through mutations or may be carried on plasmids [36].

PHARMACOKINETICS

The cephalosporins have been classified in different ways, based on chemical structure and pharmacologic activities. The conventional classification for clinical purposes groups cephalosporins into "generations" based on when they were developed and similarities in antimicrobial coverage.

First-Generation Cephalosporins

The first-generation cephalosporins are most active against aerobic gram-positive cocci. These agents include cefazolin, cephalexin, and cefadroxil, and they are often used for skin infections caused by *S. aureus* and *Streptococcus* and for susceptible urinary tract infections. They have activity against *E. coli* and some activity against *H. influenzae* and *Klebsiella* species, but because of the limited gram-negative coverage, they are not first-line agents for infections that are likely to be caused by gram-negative bacteria.

Second-Generation Cephalosporins

The second-generation cephalosporins are more active against gram-negative organisms, such as *Moraxella*, *Neisseria*, *Salmonella*, and *Shigella*. Cefoxitin and cefotetan, which are included in this group under this classification system although they are technically cephamycins, also have more coverage against anaerobic bacteria. The true cephalosporins that are also part of this class are cefprozil, cefuroxime, cefaclor, cefoxitin, and cefotetan. These drugs are used primarily for respiratory tract infections because they are better against some strains of beta-lactamase producing *H. influenzae*.

Third-Generation Cephalosporins

The third-generation cephalosporins have enhanced activity and a broader spectrum against gram-negative organisms, including *Neisseria* species, *M. catarrhalis*, *Klebsiella*, and other *Enterobacteriaceae*. Of these agents, ceftriaxone has the best activity against gram-positive cocci, specifically *S. pneumoniae* and methicillin-sensitive *S. aureus*. Ceftazidime is active against *P. aeruginosa*. Other cephalosporins in this class include cefdinir, cefditoren, cefixime, cefotaxime, cefpodoxime, ceftibuten, and ceftriaxone. These drugs are useful for more severe community-acquired respiratory, intraabdominal, and urinary tract infections and for nosocomial infections (because of the high incidence of resistant organisms) [37].

Fourth-Generation Cephalosporins

Cefepime is classed as a fourth-generation cephalosporin because it has good activity against both gram-positive and gram-negative bacteria, including *P. aeruginosa* and many *Enterobacteriaceae*. The gram-negative and anaerobic coverage makes cefepime useful for intra-abdominal infections, respiratory tract infections, and skin infections.

Fifth-Generation Cephalosporins

Ceftaroline fosamil is a novel advanced-generation cephalosporin approved by the U.S. Food and Drug Administration (FDA) in 2010, for the treatment of community-acquired bacterial pneumonia and bacterial skin and soft-tissue infections [6]. As with other beta-lactams, ceftaroline exerts its antimicrobial affect by binding to PCP and inhibiting cell wall synthesis. This agent is unique in that it also has a high affinity for PBP2a, which is associated with resistance to methicillin. Consequently, ceftaroline is highly active against methicillin-sensitive and resistant strains of *S. aureus* and against multidrug-resistant *S. pneumoniae* [38]. It is ineffective for *P. aeruginosa*, and its activity against *Enterobacteriaceae* is variable. Beta-lactamase-producing *Enterobacteriaceae* and AmpC mutants are resistant. Prospective clinical trials have shown that the efficacy of ceftaroline is comparable to vancomycin plus aztreonam for the treatment of bacterial skin and soft-tissue infection (including methicillin-resistant *S. aureus* [MRSA]) and to ceftriaxone for the treatment of community-acquired bacterial pneumonia [39]. Among cases of pneumonia caused by *S. pneumoniae*, clinical cure rates were higher with ceftaroline (83.3%) than with ceftriaxone (70%) in a phase III clinical trial, and the agent was well tolerated [40].

THE CEPHALOSPORINS					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
1st Generation					
Cefadroxil	1–2 g/day in 2 divided doses	30 mg/kg/day in 2 divided doses Max: 2 g/day	PO	Rash, diarrhea	Can interfere with some urine glucose tests.
Cefazolin	1–2 g every 8 hrs Max: 12 g/day	>1 mo: 25–100 mg/kg/day divided every 6 to 8 hrs Max: 6 g/day	IV, IM	Phlebitis at infusion site, seizure,rash, diarrhea	Can interfere with some urine glucose tests.
Cephalexin	250–1,000 mg every 6 to 12 hrs Max: 4 g/day	>1 yr to <15 yrs: 25–100 mg/kg/day in 3 to 4 divided doses Max: 4 g/day	PO	GI upset, rash	Can interfere with some urine glucose tests.
2nd Generation					
Cefaclor	250–500 mg every 8 hrs	>1 mo: 20–40 mg/kg/day in 2 to 3 divided doses Max: 1 g/day	PO	Rash, GI upset	Can interfere with some urine glucose tests.
Cefotetan	1–2 g every 12 hrs Max: 4–6 g/day	AAP recommendation: 30–50 mg/kg/dose every 12 hrs Max: 4,000 mg/day	IV, IM	Phlebitis at infusion site, rash, GI upset	Disulfiram-like reaction with alcohol. Can interfere with some urine glucose tests. Not recommended for treatment of community-acquired intra-abdominal infections.
Cefoxitin	1–2 g every 6 to 8 hrs Max: 12 g/day	>3 mos: 80–160 mg/kg/day in 4 to 6 divided doses Max: 12 g/day	IV, IM	Phlebitis at infusion site, rash	IM injection is painful. Can interfere with some urine glucose tests. In pediatrics, for group A beta-hemolytic streptococcal infections, antimicrobial therapy should be given for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis.
Cefprozil	250–500 mg every 12 to 24 hrs	>6 mos: 7.5–20 mg/kg every 12 hrs >2 yrs: 7.5–15 mg/kg/day in 2 divided doses, or 20 mg/kg every 24 hrs Max: 1 g/day	PO	Rash, GI upset, elevated liver enzymes	Avoid use in phenylketonuria. Can interfere with some urine glucose tests.
Cefuroxime	PO: 250–500 mg every 12 hrs for 10 days IV, IM: 0.5–1.5 g every 6 to 8 hrs Max: 6 g/day	PO: 20–30 mg/kg/day in 2 divided doses IV, IM: 75–150 mg/kg/day in 3 divided doses Max: 6 g/day	PO, IV, IM	Phlebitis at infusion site, rash, GI upset	Tablets and oral suspension forms require different dose. Oral doses noted here are for tablet formulation. Higher doses can be used for severe infection.
3rd Generation					
Cefdinir	300 mg every 12 hrs, or 600 mg every 24 hrs for 10 days	7 mg/kg/dose twice daily or 14 mg/kg/dose for 10 days Max: 600 mg/day	PO	Rash, diarrhea	Iron and antacids can reduce absorption. Can interfere with some urine glucose tests.
Cefditoren	200–400 mg every 12 hrs for 10 to 14 days	Not studied for patients <12 yrs	PO	GI upset, headache	Interaction with proton-pump inhibitors, H2 blockers, antacids. Contraindicated with milk protein allergy.

Table 2 continues on next page.

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THE CEPHALOSPORINS *(Continued)*					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
3rd Generation *(Continued)*					
Cefixime	400 mg/day in 1 or 2 doses	>6 mos and <45 kg: 8–20 mg/kg/day every 12 to 24 hrs Max: 400 mg/day >12 yrs or >50 kg: Use adult dosing	PO	Diarrhea, rash	Can interfere with some urine glucose tests.
Cefotaxime	1–2 g every 4 to 12 hrs	1 mo to 12 yrs and <50 kg: 50–225 mg/kg/day in 3 to 4 divided doses	IV, IM	Phlebitis at infusion site, rash, GI upset	Single dose can be given for GC. Transient arrhythmias have developed after administration of this agent through central venous catheter.
Cefpodoxime	100–400 mg every 12 hrs for 7 to 14 days	10 mg/kg/day in 2 divided doses	PO	Diarrhea, nausea, vomiting	Decreased absorption with antacids and H2 blockers. Can be given as a single dose for GC.
Ceftazidime	500–1,000 mg every 8 hrs	IV: 30–50 mg/kg every 8 hrs Max: 6 g/day AAP recommendation for IV: 90–200 mg/kg/day every 8 hours Max: 6 g/day	IV, IM	Phlebitis at infusion site, rash, GI upset	Can interfere with some urine glucose tests. The L-arginine formulation should not be used in children.
Ceftibuten	400 mg every 24 hrs for 10 days	9 mg/kg/day Max: 400 mg/day for 10 days	PO	Rash, GI upset, headache	Can interfere with some urine glucose tests.
Ceftriaxone	IV, IM: 1–2 g every 12 to 24 hrs	50–100 mg/kg/day in 1 to 2 divided doses Max: 4 g/day	IV, IM	Phlebitis at infusion site, rash	Avoid in neonates with hyperbilirubinemia. Higher doses are used for meningitis. A ceftriaxone-calcium salt can precipitate in the gallbladder, causing sonographically detectable abnormalities.
4th Generation					
Cefepime	IV: 1–2 g every 8 to 12 hrs IM: 0.5–1 g every 12 hrs	IV, IM: 50 mg/kg every 8 to 12 hrs Not to exceed adult dosing	IV, IM	Phlebitis at infusion site, GI upset	Can interfere with some urine glucose tests.
Cefiderocol	2 g every 8 hours for 7 to 10 days	—	IV	Phlebitis at infusion site, rash, GI upset	Can interfere with some urine glucose tests
5th Generation					
Ceftaroline fosamil	600 mg every 12 hours for 5 to 14 days	>2 mos to <2 yrs: 8 mg/kg dose every 8 hrs for 5 to 14 days >2 yrs to <18 yrs and <33 kg: 12 mg/kg/dose every 8 hrs for 5 to 14 days >2 yrs to <18 yrs and >33 kg: 400–600 mg every 8 to 12 hrs for 5 to 14 days	IV	Phlebitis at infusion site, GI upset, headache	Slow IV infusion over 60 minutes. Can interfere with some urine glucose tests.
Ceftobiprole	500 mg every 8 hours	—	IV	Hyponatremia, phlebitis at infusion site, headache, nausea/vomiting	Approved for use in Canada but not the United States. Not for use in patients with ventilator-associated pneumonia.

Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications.
GC = gonococcal infection.

Source: [6; 16] *Table 2*

Ceftobiprole is a fifth-generation cephalosporin with a broad spectrum of antimicrobial activity, including drug-resistant pneumococci, *P. aeruginosa*, and methicillin-resistant *S. aureus* (MRSA). The drug is approved for the treatment of community- and hospital-acquired pneumonia in Canada and parts of Europe, The results of a pivotal clinical trial of patients hospitalized with community-acquired pneumonia treated with ceftobiprole showed a high rate of clinical cure [41; 42; 43].

ABSORPTION/ELIMINATION

The orally administered cephalosporins include cefaclor, cefadroxil, cephalexin, cefprozil, cefuroxime axetil, cefixime, cefpodoxime proxetil, ceftibuten, and cefdinir. In general, the orally administered cephalosporins are absorbed rapidly. Cephalexin, cefadroxil, cefaclor, cefixime, ceftibuten, and cefdinir are nonesterified and are absorbed from the GI tract by active transport in the small intestine. Other agents, such as cefuroxime axetil and cefpodoxime proxetil, are prodrug esters and are passively absorbed. Once absorbed into the cells lining the small intestine, these agents are hydrolyzed and then excreted into the blood stream as active cephalosporins [44].

The presence of food or antacids may increase or decrease the absorption, depending on the drug. Cefuroxime axetil and cefpodoxime proxetil have increased absorption when taken with food. Cefaclor, cefadroxil, and cephalexin have slowed absorption when food is in the stomach. Cefixime, cefprozil, and ceftibuten are not affected by the presence of food. Cefpodoxime is the only cephalosporin whose absorption is decreased by the presence of antacids or H2 antagonists [45].

There is extensive distribution of the cephalosporins into body tissues and fluids. They readily cross the placenta and are also found in synovial fluid. Concentrations in bile and urine are high. Most cephalosporins do not cross into the CSF in sufficient concentration to be recommended for the treatment of meningitis, but there are some exceptions. Cefuroxime, cefotaxime, ceftriaxone, cefepime, and ceftaroline all have good penetration into the CSF [38; 46].

Most cephalosporins are eliminated by the kidney. The exception in the oral cephalosporins is cefixime, half of which is excreted in the urine [6]. The remaining half is metabolized in the liver to inactive metabolites and partly excreted in the bile. Cefotaxime is deacetylated by the liver to a bioactive metabolite and inactive forms. The deacetylated metabolites are excreted by the kidney. Cefditoren is excreted predominantly in the bile.

In severe hepatic insufficiency, compensatory changes in renal excretion of the hepatically metabolized drugs may occur [47]. In the presence of severe renal and/or hepatic insufficiency, dosage adjustment of cefotaxime is necessary.

SIDE EFFECTS/TOXICITY

As a group, cephalosporins are relatively well tolerated [48]. The most common complaints are GI upset, resulting in nausea, vomiting, or diarrhea. Thrombophlebitis can occur with intravenous (IV) administration. One to three percent of patients develop an allergic reaction. Rash, fever, eosinophilia, and urticaria can develop. Anaphylaxis is rare. Infrequently, there is some cross-sensitivity with true penicillin allergy (estimated nearly 0%to 10% of cases); this occurs mostly with first-generation cephalosporins [21; 22; 23; 24]. If a patient develops urticaria, anaphylaxis, or angioedema with penicillins or a cephalosporin, avoid using any of the other cephalosporins.

Although uncommon, nephrotoxicity has been reported [49]. Cephalosporins that contain the methylthiotetrazole (MTT) side chain (cefotetan) may induce a disulfiram-like reaction with alcohol ingestion (e.g., flushing, tachycardia, nausea and vomiting, diaphoresis, dyspnea, hypotension, and confusion). This is due to increased circulating acetaldehyde.

Ceftriaxone has been associated with cholelithiasis and cholestatic hepatitis due to precipitation in bile [50; 51]. Rare reactions include hematologic toxicity with resultant eosinophilia, thrombocytopenia, and leukopenia, all of which resolve after stopping treatment [52]. Rarely, hemolytic anemia develops [53]. Hypoprothrombinemia may occur with cephalosporins with the MTT side chain as a result of interference by the MTT moiety with the synthesis of vitamin-K-dependent clotting factors [54]. For patients at high risk of bleeding, exogenous vitamin K may help alleviate this side effect. False-positive glucosuria testing with a copper reduction test (Clinitest) may occur with many cephalosporins [6; 55].

DRUG INTERACTIONS

The serum levels of all the cephalosporins are increased with co-administration of probenecid. The effects of warfarin may be enhanced by co-administration of cefotetan, cefazolin, cefoxitin, and ceftriaxone [6].

SPECIAL POPULATIONS

Cephalosporins are generally considered safe to use in pregnancy and are designated as category B. They are excreted in breast milk in low concentrations, and the American Academy of Pediatrics (AAP) considers this compatible with breastfeeding [6; 56; 57].

CARBAPENEMS

Meropenem, imipenem/cilastatin, doripenem, and ertapenem are parenteral synthetic beta-lactams derived from thienamycin, an antibiotic produced by *Streptomyces cattleya* [58]. They have a lactam ring, like the penicillins and cephalosporins, but have a methylene moiety in the ring. The newest carbapenem is combination imipenem/cilastatin/relebactam [6].

MECHANISM OF ACTION

Like other beta-lactams, the carbapenems inhibit mucopeptide synthesis in the bacterial cell wall by binding to PBPs, leading to lysis and cell death. Bacterial resistance may occur due to a specific beta-lactamase that affects carbapenems. Another significant source of resistance is a mutation that results in

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the absence of the outer membrane porin, thus not allowing transport of the drug into the cell [59]. Cross-resistance may occur between the carbapenems.

PHARMACOKINETICS

Imipenem and ertapenem have a wide antimicrobial spectrum with excellent activity against enteric gram-negative bacilli and pseudomonas as well as anaerobic bacteria, including *Bacteroides* species. They also cover many gram-positive cocci, such as *Enterococcus* and *Streptococcus* [60]. Meropenem has somewhat greater activity against gram-negative bacteria, which are not affected by most beta-lactamases. Doripenem has good activity against *Pseudomonas aeruginosa*. Imipenem and ertapenem are approved by the FDA for use in urinary tract infections, pneumonia, intra-abdominal infections, and skin and soft-tissue infections [6]. Meropenem is approved by the FDA for treatment of intra-abdominal infections, skin and skin structure infections, and meningitis in patients older than 3 months of age [6]. Combination meropenem/vaborbactam is approved for the treatment of complicated urinary tract infections caused by susceptible micro-organisms [6; 61]. The combination imipenem/cilastatin/relebactam was approved by the FDA in 2019 for the treatment of complicated urinary tract infections and complicated intra-abdominal infections [6; 62].

ABSORPTION/ELIMINATION

Imipenem/cilastatin, imipenem/cilastatin/relebactam, meropenem, and ertapenem are given parenterally, as they are unstable in stomach acid. Imipenem is combined with cilastatin, which inhibits dehydropeptidase I in the proximal renal tubular cells. Dehydropeptidase I inactivates imipenem by hydrolysing the beta-lactam ring, so adding the cilastatin allows increased levels of imipenem in the urine and also prevents the production of the nephrotoxic metabolites of imipenem [63]. The addition of relebactam to imipenem protects imipenem from degradation by certain serine beta-lactamases [6]. Meropenem, doripenem, and ertapenem do not require a dehydropeptidase I inhibitor.

Following administration, meropenem penetrates well into body tissues and fluids, including the CSF. Imipenem/cilastatin/relebactam and ertapenem are distributed throughout body tissues, but with only low concentrations in the CSF [64].

Most of the imipenem/cilastatin and imipenem/cilastatin/relebactam doses are excreted in the urine [6]. The remaining 20% to 25% of the dose is excreted through an unknown mechanism. Meropenem is excreted unchanged into the urine by means of glomerular filtration and tubular secretion [65]. Ertapenem is metabolized by hydrolysis of the beta-lactam ring, and then both the metabolite and parent drug are excreted in the urine.

The carbapenems require dosage adjustment in patients with renal insufficiency. No changes in dosage are necessary for patients with hepatic insufficiency.

SIDE EFFECTS/TOXICITY

The carbapenems are generally well tolerated. Occasional reactions include nausea and vomiting, phlebitis at the infusion site, elevation of liver enzymes, and leukopenia. Seizures may occur. The risk is higher in patients with underlying central nervous system (CNS) disease and in patients with renal disease, which results in high serum levels of the drug [66]. Hypersensitivity reactions may occur, and while there is a degree of cross-sensitivity with penicillins, this risk is lower than previously believed [22; 23; 24]. Carbapenems should be used with caution in patients allergic to the carbapenems or penicillins [6].

DRUG INTERACTIONS

There are few drug interactions associated with the carbapenems, but probenecid may increase the serum levels of meropenem, ertapenem, imipenem/cilastatin, and imipenem/cilastatin/relebactam and should be avoided. Ertapenem cannot be infused with dextrose or other medications. Meropenem may reduce levels of valproic acid [67].

SPECIAL POPULATIONS

Meropenem, doripenem, and ertapenem are pregnancy category B, with animal studies showing no adverse reactions [68]. Imipenem/cilastatin is pregnancy category C, based on studies in monkeys that showed increased embryonic loss and side effects in the mother [69]. No pregnancy category has been assigned to imipenem/cilastatin/relebactam [6; 70]. No data are available regarding breastfeeding and carbapenem administration.

The safety of doripenem use has not been studied in children. Meropenem has been used in children and is indicated by the FDA for the treatment of pediatric meningitis but has not been studied in infants younger than 3 months of age [6; 71]. Ertapenem can be used in infants older than 3 months of age, and imipenem can be used from birth; these agents are useful for treating complicated infections in pediatric patients (e.g., complicated urinary tract infections).

MONOBACTAMS

Monobactams have a single beta-lactam core, distinguishing them from the other beta-lactam drugs [72]. Aztreonam is the only available example of this class of drugs. Aztreonam was originally extracted from *Chromobacterium violaceum*. It is now manufactured as a synthetic antibiotic.

MECHANISM OF ACTION

As with other beta-lactams, aztreonam inhibits mucopeptide synthesis in the bacterial cell wall by binding to the penicillin-binding proteins of gram-negative bacteria, leading to cell lysis and death. Aztreonam is resistant to most beta-lactamases. Treatment in combination with an aminoglycoside appears to be synergistic against *Pseudomonas*.

THE OTHER BETA-LACTAMS					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Carbapenems					
Doripenem	500 mg every 8 hours for 5 to 14 days	Not studied for pediatric use	IV	Headache, rash, nausea, vomiting, diarrhea, phlebitis	Dosage adjustment necessary for renal impairment. Cannot be used in patients with known serious hypersensitivity or history of anaphylaxis to any beta-lactam antibiotic. Seizure risk in patients with CNS disorders.
Ertapenem	1 g/day for 3 to 14 days	15 mg/kg every 12 hrs Max: 1 g/day for 3 to 14 days	IV, IM	Diarrhea, nausea, phlebitis at infusion site	Seizure risk in patients with CNS disorders. IV therapy may be administered for up to 14 days; IM for up to 7 days.
Imipenem/ cilastatin	500–1,000 mg every 6 to 8 hrs Max: 4 g/day	>3 mos: 15–25 mg/kg every 6 hrs Max: 4 g/day	IV	Phlebitis at infusion site, rash	Documentation of cross-allergy with penicillin allergy is limited. Seizure risk in patients with CNS disorders. Adults <70 kg may require decreased dosing.
Imipenem/ cilastatin/ relebactam	1.25 g every 6 hours for a 5-14 days	N/A	IV	Anemia	Documentation of cross-allergy with penicillin allergy is limited. Seizure risk in patients with CNS disorders.
Meropenem	1.5–6 g/day in 3 divided doses	Infants <3 mos (IV): Gestational age <32 weeks AND postnatal age <14 days: 20 mg/kg/dose every 12 hrs Postnatal age ≥14 days: 20 mg/kg/dose every 8 hrs Gestational age ≥32 weeks AND postnatal age <14 days: 20 mg/kg/dose every 8 hrs Postnatal age ≥14 days: 30 mg/kg/dose every 8 hrs >3 mos and <50 kg: 30–120 mg/kg/day in 3 divided doses Max: 6 g/day >50 kg: Same as adult dosing	IV	Diarrhea, nausea, inflammation at the injection site, headache	Can cause elevated LFTs. Seizure risk in patients with CNS disorders.
Meropenem/ vaborbactam	4 g every 8 hrs for <14 days	Not studied in pediatric patients	IV	Headache, GI symptoms, phlebitis at infusion site	Dosage adjustment necessary for renal impairment.
Monobactams					
Aztreonam	IV: 1–2 g every 8 to 12 hrs Nebulizer: 75 mg 3 times/day at least 4 hours apart for 28 days; do not repeat for 28 days after completion.	>9 mos: 30–50 mg/kg/dose every 6 to 8 hrs Max: 120 mg/kg/day >7 years of age (nebulizer): Same as adult dosing	IV, IM, oral inhalation	Rash, nausea, vomiting, phlebitis at infusion site	Rare cross-sensitivity with allergy to other beta-lactams. For oral inhalation, pretreatment with a bronchodilator is recommended.

Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications.
CNS = central nervous system; LFTs = liver function tests (liver enzymes).

Source: [6; 16] *Table 3*

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PHARMACOKINETICS

Aztreonam does not have significant activity against gram-positive or anaerobic bacteria and is primarily used as an alternative therapy for gram-negative bacterial infections, including *P. aeruginosa* and *Klebsiella*, that are resistant to the first-line beta-lactams or carbapenems. It is indicated for use in pneumonia, soft-tissue infections, urinary tract infections, and intra-abdominal and pelvic infections that are caused by gram-negative aerobic bacteria.

There is no oral form of aztreonam, and intravenous is the preferred mode of parenteral administration. It is distributed widely in body tissues and fluids, including inflamed meningeal tissue [6; 73]. Aztreonam is mainly excreted in the urine as an unchanged drug, although there is also minimal hepatic metabolism [6; 74]. Doses must be adjusted for renal insufficiency based on glomerular filtration rate [6; 75].

SIDE EFFECTS/TOXICITY

Frequent adverse reactions include elevations of liver enzymes and transient eosinophilia. Less common reactions include phlebitis at the infusion site, rash, diarrhea, and nausea [6; 76].

There have been a few reports of cross-allergy reactions in patients who are allergic to ceftazidime, but patients with penicillin and cephalosporin allergy can usually tolerate aztreonam [77]. Aztreonam is contraindicated in patients with prior allergic reactions to it or to any component of the formulation.

DRUG INTERACTIONS

No drug interactions have been reported with aztreonam [6; 78].

SPECIAL POPULATIONS

Aztreonam is pregnancy category B, based on animal studies that have shown no ill effects of the drug. There are no human data available [6].

Aztreonam is secreted in breast milk in low concentrations; breastfeeding is not recommended because the effects of the drug have not been studied in young infants [78].

Aztreonam has not been studied for use in children younger than 1 month of age but appears safe in children older than 1 month of age, although it should be noted that manufacturer recommendations are for children older than 9 months of age [6; 78]. It has been shown to be very useful in children with respiratory symptoms of cystic fibrosis [79].

AMINOGLYCOSIDES

The first aminoglycoside, streptomycin, was derived from *Streptomyces griseus* during the 1940s. Actinomycetes were studied for possible antimicrobial byproducts, and it was found that *Micromonospora* and *Streptomyces* produced useful agents. As newer, safer, and more effective aminoglycosides have been developed, the use of streptomycin is now confined primarily to certain management strategies for the treatment of tuberculosis.

MECHANISM OF ACTION

The basic structure of the aminoglycosides is an aminocyclitol ring. Different members of the family have different glycosidic linkages and side groups.

The aminoglycosides have at least two effects on the bacterial cell that ultimately result in cell death. These agents bind negative charges in the outer phospholipid membrane, displacing the cations that link the phospholipids together. This leads to disruption in the wall and leakage of cell contents. In addition, they inhibit protein synthesis by binding to the 30S subunit of the ribosome, causing miscoding and termination [80].

Although resistance to aminoglycosides is less common than with many other antibiotics, it can develop as a result of three known mechanisms. The most common pattern of resistance involves modification of the aminoglycoside molecule itself by enzymes produced by some bacteria. After the aminoglycoside is altered, it cannot bind as well to the ribosomes. The genes that encode for these enzymes are carried on plasmids, allowing rapid transfer of resistance between bacteria. Of note, amikacin has an S-4 amino 2-hydroxybutyryl (AHB) side chain that protects it against deactivation by many bacterial enzymes and is therefore less susceptible to this bacterial defense mechanism [81].

The binding site for aminoglycosides on the rRNA of the ribosome may also be altered, reducing binding. In addition, mutations that cause reduced uptake of aminoglycosides have been documented [81].

To combat resistances and overcome the relative natural resistance of enterococcus, other agents that target the cell wall are often used in conjunction with the aminoglycosides. Damage to the cell wall from the additional agents may be bactericidal in some cases and makes the cell wall more permeable to the aminoglycosides [82].

PHARMACOKINETICS

The aminoglycosides are effective for the treatment of aerobic gram-negative bacilli, such as *Klebsiella* species, *Enterobacter*, and *P. aeruginosa*. There is very little activity against anaerobes and gram-positive organisms, so combination therapy with a beta-lactam, vancomycin, or other agents active against gram-positive organisms and anaerobes is commonly used. The aminoglycosides are indicated for infections caused by susceptible organisms of the urinary tract, respiratory tract, skin and soft tissues, and sepsis due to gram-negative aerobic bacilli.

The aminoglycosides commonly used at present for treatment of systemic bacterial infection include gentamicin, tobramycin, and amikacin. Kanamycin is discontinued [17]. Aminoglycosides have negligible oral absorption and thus require parenteral administration. They also can be administered directly

THE AMINOGLYCOSIDES					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Amikacin	5 mg/kg every 8 hrs or 7.5 mg/kg every 12 hrs	15–22.5 mg/kg/day every 8 hrs OR 15–20 mg/kg/dose every 24 hours	IV, IM	Renal failure, vestibular nerve damage, auditory nerve damage	Predisposition to auditory/vestibular nerve damage may be genetic; check family history. Check serum levels. Doses are based on lean body mass; maintenance dose is based on calculation with creatinine clearance. Additional dose adjustments are needed in renal failure.
Gentamicin	3–5 mg/kg/day in divided doses every 8 to 12 hrs, or 5–7 mg/kg once daily	Infants: 2–2.5 mg/kg/dose every 6 to 8 hrs	IV, IM, topical		
Neomycin	4–12 g/day in 4 to 6 divided doses for 5 to 6 days, or 4 g/day for an indefinite period	50–100 mg/kg/day in 3 to 4 divided doses	PO, topical	Systemic absorption is possible, resulting in the same side effects as amikacin.	Used as a bowel prep for surgery. Is also formulated in some topical eye, ear, and skin preparations.
Plazomicin	15 mg/kg once daily for 4-7 days	N/A	IV	Renal failure	Boxed warning: Risk factors for nephrotoxicity include pre-existing renal impairment, elderly patients, concomitant. May cause ototoxicity; symptoms may be irreversible and may not become evident until after therapy is complete.
Streptomycin	15–30 mg/kg/day or 1–2 g daily	20–40 mg/kg/day every 6 to 12 hrs in divided doses Max: 1 g/dose or 2 g/day	IM	Renal failure, vestibular nerve damage, auditory nerve damage	This is the most ototoxic of aminoglycosides; levels must be monitored closely. Can cause neuromuscular blockade and respiratory paralysis, especially when given soon after muscle relaxants or anesthesia.
Tobramycin	1–2.5 mg/kg every 8 to 12 hrs. or 4–7 mg/kg once daily dose	<5 yrs: 2.5 mg/kg every 8 hrs >5 yrs: 2–2.5 mg/kg every 8 hrs	IV, IM inhalation solution, ophthalmic ointment or solution	Renal failure, vestibular nerve damage, auditory nerve damage	Effects of nondepolarizing muscle relaxants can be increased. Total body weight (as opposed to ideal body weight) should be used for underweight patients.
Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications.					
Source: [6; 16]					*Table 4*

into body cavities and have a role in the management of pleural and peritoneal infection. Tobramycin is particularly useful for treatment of recurrent *Pseudomonas* infection in patients with cystic fibrosis and can be administered by aerosolized inhalation to facilitate optimal local antimicrobial effect [79]. In a large randomized, placebo-controlled clinical trial involving critically ill adults who had undergone invasive mechanical ventilation, a three-day prophylactic regimen of inhaled amikacin reduced the subsequent incidence of ventilator-associated pneumonia [174]. Neomycin is often used orally as part of a pre-operative bowel decontamination protocol.

The aminoglycosides are widely distributed in extracellular fluid, including pleural fluid, synovial fluid, abscesses, and peritoneal fluid. They are relatively insoluble in lipid, so the volume of distribution is lower in obese patients. They have poor distribution in bile, aqueous humor, bronchial secretions, sputum, and the CSF [15].

Aminoglycosides are excreted unchanged by the kidneys [6]. There is no reduction of dosage necessary in liver failure, as there is no hepatic metabolism of these agents. In renal failure, the dosage must be carefully adjusted based on glomerular filtration rate and measured serum levels. Serum levels should be monitored in all patients with reduced renal function [83].

TOXICITY

The most common adverse effect associated with aminoglycoside usage is nephrotoxicity, occurring in 10% to 25% of therapeutic courses [84]. Aminoglycosides are freely filtered by the glomeruli and quickly taken up by the proximal tubular epithelial cells, where they exert their main toxic effect by altering

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phospholipid metabolism. Aminoglycosides also cause renal vasoconstriction [85]. Critical factors in the development of acute kidney injury secondary to aminoglycoside nephrotoxicity are dosing and duration of therapy. A single daily large dose is preferable to more frequent dosing, as it appears to cause less accumulation in the tubular cells once the saturation point is reached [84]. Additionally, extending the dose interval to more than 24 hours in patients with renal impairment has been found to be effective, with irreversible nephrotoxicity reported in only 1% of patients studied [86].

Vestibular and auditory toxicity may also complicate treatment with aminoglycosides, though this is less common now as clinical awareness and careful dosage adjustment in relation to renal function has improved. These effects are usually reversible, and because there is some data suggesting that there is a genetic predisposition to ototoxicity, this drug class should be avoided in patients who have a family history of ototoxicity with aminoglycosides [87]. When aminoglycoside therapy is expected to exceed five to seven days, baseline testing of auditory function should be performed and monitored weekly for the duration of treatment.

Neuromuscular blockage has also been observed as a side effect. Aminoglycosides may aggravate muscle weakness in patients with neuromuscular disorders, such as myasthenia gravis and Parkinson disease, due to a curare-like effect on neuromuscular function [88].

Hypersensitivity reactions are not common with aminoglycosides, but rash, fever, urticaria, angioneurotic edema, and eosinophilia may occur. Very rare reactions include optic nerve dysfunction, peripheral neuritis, arachnoiditis, encephalopathy, pancytopenia, exfoliative dermatitis, and amblyopia. Bronchospasm and hoarseness have been known to occur with tobramycin inhalation solution [89].

The aminoglycosides are contraindicated in patients with hypersensitivity to the drug. Cross-sensitivity between aminoglycosides does occur. Streptomycin also contains metabisulfite and should be avoided if the patient is allergic to sulfites (more common in asthmatics) [6; 90].

DRUG INTERACTIONS

There are numerous drug interactions that should be taken into consideration when using the aminoglycosides. The risk of nephrotoxicity may be increased with co-administration of other drugs that are nephrotoxic or in patients receiving loop diuretics (e.g., furosemide). Respiratory depression may occur if aminoglycosides are given with nondepolarizing muscle relaxants. Neomycin may affect digoxin levels by altering the bowel flora responsible for the metabolism of digoxin in the GI tract. Gentamicin may also cause increased serum digoxin levels [6; 91].

In vitro deactivation of penicillins due to acylation has been observed, so the drugs should not be mixed in vitro. Tobramycin inhalation solution cannot be mixed in the nebulizer with dornase alfa [6].

SPECIAL POPULATIONS

Amikacin, gentamicin, neomycin, and streptomycin are pregnancy category D due to eighth cranial nerve toxicity that has occurred in the fetus with some aminoglycosides [6]. Plazomicin and tobramycin carry a boxed warning that states pregnant patients should be apprised of potential harm to the fetus with their administration [6].

Traces of amikacin, gentamicin, streptomycin, and tobramycin are excreted in breast milk, but they are compatible with breastfeeding because they are very poorly absorbed from the GI tract [6]. However, they may cause alterations in the normal bowel flora of the infant [6]. It is not known if neomycin or plazomicin are present in breast milk [6].

Half-life alterations occur in patients at extremes of age. The half-life in neonates and low-birth-weight infants may be considerably prolonged. The elderly may also have a longer aminoglycoside half-life due to an age-related decrease in renal function [92]. Geriatric dosing should be based on ideal body weight estimates [6].

MACROLIDES

The original macrolide, erythromycin, was discovered in 1952 by J.M. McGuire. It is produced by *Saccharopolyspora erythraea* (formerly known as *Streptomyces erythreus*). Semisynthetic derivatives (clarithromycin, azithromycin) have been produced from the original erythromycin, with modifications that improve acid stability, antibacterial spectrum, and tissue penetration.

MECHANISM OF ACTION

The macrolides are bacteriostatic, inhibiting protein synthesis by binding at the 50S ribosomal unit and by blocking transpeptidation and translocation. At high concentrations or with rapid bacterial growth, the effects may be bactericidal [93]. Data challenge the view of macrolides as global inhibitors of protein synthesis. Evidence demonstrates that these agents selectively inhibit the translation of a subset of cellular proteins, that they impact protein synthesis in a context-specific manner, and that they manifest site specificity of action [94; 95; 96; 97; 98].

Many bacteria that are resistant to the penicillins are also resistant to erythromycin. Bacterial resistance may result from decreased permeability of the cell membrane; in addition, an increase in active efflux of the drug may occur by incorporating a transporter protein into the cell wall [98; 99; 100].

The gene for this mechanism is transferred on plasmids between bacteria. Mutations of the 50S ribosomal receptor site may also develop, preventing binding of the erythromycin [101]. Lastly, bacterial enzymes have been described that may deactivate erythromycin [102]. It is likely that this form of resistance is also transferred on plasmids.

THE MACROLIDES					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Azithromycin	PO: 250–600 mg/day, or 1–2 g/day IV: 250–500 mg/day	PO: 5–12 mg/kg/day Max: 500 mg/day Otitis media: 30 mg/kg as single dose (not to exceed 1,500 mg)	PO, IV, ophthal-mic drops	GI upset	One dose of 1 g given PO can be used for non-GC urethritis/cervicitis. Interaction with pimozide/cyclosporine.
Clarithromycin	250–500 mg every 12 hrs, or 1 g/day extended-release formulation for 7 to 14 days	>6 mos of age: 7.5 mg/kg every 12 hrs	PO	GI upset, metallic taste	Inhibits liver CYP 450 enzyme 3A4, resulting in multiple significant drug interactions. Special dosing combined with omeprazole and amoxicillin or lansoprazole and amoxicillin is one regimen used for *H. pylori* treatment.
Erythromycin	Base: 250–500 mg PO every 6 to 12 hrs Max: 4 g/day Ethylsuccinate: 400–800 mg PO every 6 to 12 hrs Max: 4 g/day Lactobionate: 15–20 mg/kg/day IV in 4 divided doses, or 0.5–1 g IV every 6 hrs, or continuous infusion over 24 hrs (Max: 4 g/day)	Base: 30–50 mg/kg/day PO in 2 to 4 divided doses Max: 2 g/day Ethylsuccinate: 30–50 mg/kg/day PO in 2 to 4 divided doses Max: 4 g/day Stearate: 30–50 mg/kg/day PO in 2 to 4 divided doses Max: 2 g/day Lactobionate: 15–50 mg/kg/day IV in 4 divided doses Max: 4 g/day	PO, IV, ophthalmic solution, topical ointment, gel, or pad	GI intolerance (common), phlebitis at IV infusion site	Inhibits liver CYP 450 enzymes 3A4 and 1A2, resulting in multiple significant drug interactions.
Fidaxomicin	200 mg twice daily for 10 days	Not studied in pediatric patients	PO	Nausea, abdominal pain	Used for treatment of diarrhea due to *C. difficile*

Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications.
Non-GC = nongonococcal infection.

Source: [6; 16] *Table 5*

Many strains of *H. influenzae* are resistant to erythromycin alone but are susceptible to a combination with a sulfonamide [103]. Erythromycin ethylsuccinate and sulfisoxazole are manufactured as suspensions for use in treating acute otitis media in children older than 2 months of age [6]. They are useful for targeting *H. influenzae*, one of the common pathogens in otitis media in this age group.

PHARMACOKINETICS

Erythromycin has a wide spectrum of activity. Gram-positive bacteria that are usually susceptible to erythromycin include the *Streptococcus* species. Erythromycin is a second-line agent for gram-negative bacteria, such as *H. influenzae* (when used concomitantly with sulfonamides) and *M. catarrhalis*. Macrolides are particularly useful for their coverage of atypical bacteria, such as *Mycoplasma* and *Chlamydia*. Some spirochetes and mycobacteria are also susceptible to the macrolides. These drugs are indicated for upper respiratory tract infections, such as sinusitis, otitis media, pharyngitis, and bronchitis. They are also useful in the treatment of pertussis, Legionnaires disease, and diphtheria.

Macrolides are relatively poorly absorbed orally. Fidaxomicin is minimally absorbed and active only locally in the gastrointestinal tract. Food increases absorption of extended-release clarithromycin but has little or no effect on the immediate-release preparation of the drug. Food causes decreased absorption of both azithromycin capsules and erythromycin (including base and stearate formulations) [104]. Erythromycin may also be given intravenously.

All the macrolides have extensive tissue distribution, with less than adequate penetration into the brain tissue and the CSF [104]. Erythromycin is primarily excreted in feces and urine, with 2% to 15% unchanged [6]. Azithromycin is primarily

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excreted unchanged into the bile. Clarithromycin is excreted in the urine, both unchanged and as the hydroxy metabolite.

It may be necessary to adjust the doses of the macrolides in the presence of severe hepatic insufficiency. Azithromycin should be used with caution in adults with hepatic impairment; no dosage adjustments are recommended for renal impairment [6]. A dosage adjustment of clarithromycin may be appropriate in patients with hepatic impairment and concomitant severe renal impairment; clarithromycin doses may have to be reduced in severe renal failure [6].

SIDE EFFECTS/TOXICITY

While serious side effects with the macrolides are rare, milder side effects are common. Erythromycin stimulates motility in the GI tract, and this may cause abdominal cramping, diarrhea, nausea, and vomiting. Hepatic dysfunction with or without jaundice has occasionally been reported with erythromycin estolate. There have also been some reports of reversible hearing loss in patients treated with erythromycin in high doses or in the presence of renal insufficiency. With IV erythromycin, prolongation of the QT interval and ventricular tachycardia may occur [104].

Clarithromycin may cause nausea, diarrhea, abnormal taste, dyspepsia, and headache. There have been reports of tooth discoloration that is reversible with professional cleaning. Transient CNS changes with anxiety and behavioral changes, which resolve when the drug is discontinued, have also been reported [105].

Allergic reactions to macrolides are rare but may include rash and eosinophilia. Very rarely, severe reactions such as Stevens-Johnson syndrome have occurred. The drugs are contraindicated in patients with known hypersensitivity to the macrolides.

DRUG INTERACTIONS

Drug interactions are extensive. Erythromycin and clarithromycin are inhibitors and substrate for the 3A isoform subfamily of the cytochrome P450 enzyme system (CYP3A4). If they are given with a drug that is primarily metabolized by CYP3A, the drug serum levels may be increased and/or prolonged [6]. Erythromycin is contraindicated with concurrent use of cisapride, pimozide, dihydroergotamine, ergotamine, lovastatin, simvastatin, astemizole, or terfenadine. Clarithromycin is contraindicated with concurrent use of cisapride, pimozide, ergot alkaloids (e.g., ergotamine), or lomitapide [6]. Serum levels of theophylline, cyclosporine, ergotamine, carbamazepine, benzodiazepines, warfarin, amiodarone, and tacrolimus may also be affected by concurrent administration with erythromycin and clarithromycin. Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors levels may also be elevated, with increased risk for rhabdomyolysis [6; 106].

Azithromycin is not likely to interact with drugs metabolized by CYP3A4. However, azithromycin interacts with pimozide, potentially resulting in QT interval prolongation and arrhythmia [107]. Co-administration with pimozide is therefore contraindicated. Levels of cyclosporine could potentially be increased and therefore should be monitored closely [6; 108].

SPECIAL POPULATIONS

Erythromycin is pregnancy category B, with an erythromycin estolate preparation as the preferred form because it is less likely to cause hepatotoxicity. Surveillance studies have not shown any increase in adverse outcomes. Azithromycin is also category B [6]. The CDC recommends the use of azithromycin for the treatment of *Chlamydia* during pregnancy. Treatment with erythromycin is an approved alternative regimen [109].

Clarithromycin is pregnancy category C, based on the finding that it causes growth retardation in monkeys and adverse effects on other mammals, including fetal loss. A postmarketing surveillance study did not find any evidence of teratogenicity, but a Danish study found a doubling in the frequency of miscarriages among women treated with clarithromycin [110; 111]. The manufacturer recommends that clarithromycin not be used in pregnant women unless there are no alternative therapies [6].

Erythromycin is excreted in breast milk, but the AAP considers it usually compatible with breastfeeding [57]. Clarithromycin is excreted in breast milk, but breastfeeding is considered acceptable when the relative infant dose is less than 10% [112]. One systematic review and meta-analysis demonstrated a significant association between post-natal use of erythromycin and infantile hypertrophic pyloric stenosis [113].

QUINOLONES

The first quinolone, nalidixic acid, was introduced in 1962. It was developed as a result of chloroquine synthesis. Later, derivatives with broader spectrum antimicrobial coverage were produced, leading to the current class of quinolone drugs (fluoroquinolones). As with other classes of synthetic and semisynthetic antimicrobials, alterations of side chains affect antimicrobial activity and pharmacokinetics [114].

MECHANISM OF ACTION

Quinolones inhibit DNA gyrase and DNA topoisomerase, enzymes that mediate DNA supercoiling, transcription, and repair [6; 115]. Quinolones convert these enzymes into cellular toxins, inhibit replication of bacterial DNA by blocking and/or inhibiting the enzymes, relax DNA supercoils, and enable DNA replication and repair. The interference with replication and transcription processes can lead to permanent chromosomal breaks. If the breaks overwhelm the SOS response and other DNA repair pathways, cell death can occur [116; 117].

Bacterial resistance develops as a result of spontaneous mutations that change the binding sites for quinolones on the DNA gyrase and the DNA topoisomerase [116]. Mutations that decrease the ability of quinolones to cross the cell membrane also occur. Plasmids that carry quinolone resistance genes have been identified as an emerging clinical problem [117; 118].

THE QUINOLONES					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Besifloxacin	1 drop 3 times daily (4 to 12 hrs apart) for 7 days	Same as adult dosing	Ophthalmic drops	Headache	Contact lenses should not be worn during treatment
Ciprofloxacin	PO: 250–750 mg every 12 hrs IV: 200–400 mg every 12 hrs	PO: 20–30 mg/kg/day in 2 divided doses Max: 1.5 g/day IV: 20–30 mg/kg/day in 2 divided doses Max: 800 mg/day	PO, IV, topical, otic, ophthalmic solution or ointment	GI upset, headache	Photosensitivity can occur. Antacids decrease absorption. Can prolong QT interval. Quinolones may cause tendon inflammation and rupture and may exacerbate myasthenia gravis associated muscle weakness.
Delafloxacin	PO: 450 mg every 12 hrs for 5 to 14 days IV: 300 mg every 12 hrs for 5 to 14 days	Not studied in pediatric patients	PO, IV	GI upset, increased serum transaminases	
Gatifloxacin	Days 1 and 2: 1 drop every 2 hrs while awake Max: 8/day Days 3–7: 1 drop 2 to 4 times/day	>1 yr: same as adult dosing	Ophthalmic drops	Headache, GI upset, conjunctival irritation, keratitis	
Levofloxacin	250–750 mg/day for 5 to 14 days	N/A	PO, IV, ophthmalmic drops, inhalation	GI upset, headache, phototoxicity	
Moxifloxacin	400 mg/day for 5 to 14 days	N/A	PO, IV, ophthalmic drops	GI upset, headache	
Ofloxacin	200–400 mg every 12 hrs	N/A	PO, otic, ophthalmic drops	GI upset, headache	
Ozenoxacin	Apply thin layer to affected area (up to 100 cm^2) twice/day for 5 days	Infants >2 mos to 12 yrs: Same as adult dosing, except treated area may only be up to 2% of total body surface area (Max: 100 cm^2) >12 yrs: same as adult dosing	Topical	<1% experience rosacea-like face eruption, seborrheic dermatitis	Novel drug for treatment of impetigo caused by *Staphylococcus aureus* or *Streptococcus pyogenes*
Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications.					
Source: [6; 16]					*Table 6*

PHARMACOKINETICS

The quinolones are active against many gram-positive cocci, gram-negative bacilli, and atypical bacteria (e.g., *Legionella*, *Mycoplasma*). Older quinolones have poor activity against streptococci and anaerobes, at achievable serum levels, is relatively poor, although newer agents, such as moxifloxacin, have better coverage against streptococci (including *S. pneumoniae* with reduced penicillin sensitivity) and some anaerobes [119]. Gram-negative coverage includes *Campylobacter*, *Enterobacter*, *E. coli*, *H. influenzae*, *Klebsiella*, *Salmonella typhi*, *Shigella*, and *Vibrio cholerae* [119]. Indications for the use of quinolones include urinary tract infections, non-gonococcal infections of the urethra and cervix, pneumonia, sinusitis, soft-tissue infections, and prostatitis. Ciprofloxacin is indicated for post-exposure prophylaxis for anthrax, and levofloxacin has an indication for the treatment of inhalation anthrax infection [6]. The quinolones are absorbed well after oral administration, and peak serum levels in the elderly and those with reduced renal function approximate those achieved with intravenous usage. Food may delay the time to reach peak serum concentration but does not decrease total absorption. Oral absorption is

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diminished by coadministration of aluminum, magnesium, calcium, zinc, and/or iron preparations [119]. The drugs are distributed well throughout all tissues, including the prostate, although the levels in the CSF and prostatic fluid are lower than serum levels [6].

Most quinolones are metabolized in the liver and excreted in the urine, reaching high levels in urine. Moxifloxacin is mainly excreted nonrenally. It is metabolized, via glucuronide and sulfate conjugation in the liver, to an inactive metabolite [6; 119; 120]. Ciprofloxacin has a mixed route of elimination. As much as 35% to 70% of the ciprofloxacin dose is excreted renally [6].

In renal insufficiency, the quinolones that are primarily excreted renally and those with mixed routes of elimination require dosage adjustments [6]. Moxifloxacin doses do not have to be adjusted for mild hepatic insufficiency [6].

SIDE EFFECTS/TOXICITY

The most common side effect with the use of quinolones is GI upset. Less common side effects include headache, insomnia, dizziness, peripheral neuropathy, tendon rupture, elevated liver enzymes, and interstitial nephritis [6; 121; 122]. Rarely, hematologic toxicities have occurred, resulting in hemolytic anemia (more likely to occur in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency), aplastic anemia, and agranulocytosis [123]. Very rarely, hepatic necrosis and hepatic failure have been reported [6; 124].

Although allergic reactions are not common, they may occur and range from a rash to severe reactions, such as Stevens-Johnson syndrome. Very rare cases of severe fatal hypoglycemia have been reported with concurrent treatment with glyburide and ciprofloxacin [125]. Use quinolones with caution in patients with medical problems that predispose the patient to seizures. Quinolones should not be used in patients with CNS disorders [119].

There is also a risk of disabling peripheral neuropathy associated with the use of oral or injectable fluoroquinolones [126]. The onset can be rapid, and patients should be advised to contact their healthcare provider if any signs or symptoms develop. In these cases, the fluoroquinolone should be stopped and an alternative non-fluoroquinolone drug used, unless the benefit of continued treatment outweighs the risk [119; 126].

In 2018, the FDA strengthened the warnings about the risks of mental health side effects (e.g., disorientation, agitation, delirium) and serious blood sugar disturbances (including hypoglycemia coma) associated with fluoroquinolones [127].

DRUG INTERACTIONS

Drug interactions are common and vary among the quinolones. Antacids may decrease the absorption of these agents. Iron supplements and other supplements with divalent and trivalent cations cause quinolone-cation complexes and impair absorption [119; 128]. Concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) appears to increase the risk of seizures [6; 129].

Theophylline, phenytoin, and warfarin levels may be elevated in patients concurrently treated with ciprofloxacin. Serum levels or prothrombin time should be monitored, and the doses of these drugs should be altered as appropriate [6]. Dosage adjustments are not typically needed with other quinolones [119].

SPECIAL POPULATIONS

Quinolones should be used in pregnancy only if clinical benefit exceeds risk and a safer alternative is not available [119]. Because quinolones enter breast milk, their use during breastfeeding should be avoided if alternative agents are available [119].

Quinolones are not routinely used as first-line therapy for pediatric patients but may be considered a reasonable alternative in situations where no safe and effective substitute is available (e.g., multi-drug resistance) [6].

SULFONAMIDES

Sulfonamides, the first true antibiotics, are derived from azo dyes. The first agent was sulfachrysoidine, used in 1935, which released sulfanilamide in vivo [130]. Modifications were made to the sulfanilamide to reduce side effects, resulting in the development of the modern sulfonamides. Many of the sulfonamides are no longer used as parenteral agents, but they continue to be used as topical agents or for treatment in specific conditions (e.g., prophylaxis for drug-resistant malaria). Some of these agents are no longer available in the United States but are still commonly used in other countries.

MECHANISM OF ACTION

The sulfonamides are bacteriostatic, exerting their effect as competitive antagonists of para-aminobenzoic acid (PABA). They inhibit dihydropteroate synthase from using PABA to synthesize dihydropteroic acid, a precursor of folic acid. The lack of folic acid intermediates ultimately results in impaired synthesis of nucleotides. Bacteria that use pre-formed folate are not susceptible to the bacteriostatic action. Silver sulfadiazine is one exception, as it exerts its effects on the cell membrane and cell wall and is bactericidal.

Unfortunately, bacterial resistance to sulfonamides is common, with cross-resistance between agents frequently occurring [131]. Mutations that result in additional production of PABA or changes in the enzyme binding sites for sulfonamides are responsible for the resistance [132; 133]. Genes for these resistant mutations may be carried on plasmids, allowing rapid transfer to other similar bacteria and resulting in more rapid development of resistance patterns than through random mutation alone [133; 134].

One method for improving bacterial activity against potentially resistant strains is the addition of trimethoprim [135]. Trimethoprim is a competitive inhibitor of dihydrofolate reductase, another enzyme active in the synthesis of folate [6]. Trimethoprim resistance is also common [136].

PHARMACOKINETICS

The sulfonamides can be divided into groups based on absorption and excretion characteristics. They are classified as short- to medium-acting agents, agents limited to activity in the GI tract, and topical agents.

The Short- to Medium-Acting Sulfonamides

This group of agents includes sulfadiazine and sulfamethoxazole. Sulfadiazine is readily diffused into CSF and excreted largely in urine, 15% to 40% as metabolites and 43% to 60% as unchanged drug [6]. It is indicated for use in treating chancroid, trachoma, inclusion conjunctivitis, nocardiosis, UTIs, toxoplasmosis encephalitis, and malaria and for prophylaxis of rheumatic fever [6]. Sulfamethoxazole is combined with trimethoprim and is indicated for *Pneumocystis jiroveci* prophylaxis and treatment, upper respiratory tract infections, and urinary tract infections [6].

Sulfonamides Limited to Gastrointestinal Tract Activity

The agents limited to the GI tract are very poorly absorbed and have been used for reducing bacterial flora in the bowel before surgery. The only available agent in this class is sulfasalazine, which is used in the treatment of ulcerative colitis and for juvenile and rheumatoid arthritis in patients who have responded inadequately to salicylates or other NSAIDs [6]. Although absorption of sulfasalazine from the intact intestine is very low, inflammation in the bowel may result in significant absorption of the metabolite sulfapyridine [6].

Topical Sulfonamides

The topical sulfonamides include mafenide acetate and silver sulfadiazine, which are used in the treatment of burns. Mafenide is used less often because it may cause a metabolic acidosis as a result of carbonic anhydrase inhibition. An additional topical agent is sulfacetamide, which is used in ophthalmic and lotion formulations. Topical sulfonamides may be absorbed systemically, and if large burn areas are treated, absorption may be significant [6].

ABSORPTION/ELIMINATION

The sulfonamides are quickly absorbed after administration unless they have been altered to stay in the lumen of the intestine (e.g., sulfasalazine). After absorption, they are acetylated in the liver into a toxic but inactive form. The acetylated form is mostly excreted in the urine, with a small amount excreted in bile. These drugs are widely distributed throughout body tissue and fluids, including the CSF and peritoneal fluid [137].

The sulfonamides undergo acetylation and glucuronidation in the liver. Both the unchanged and metabolized forms are excreted in the urine through glomerular filtration and renal tubular secretion.

Mafenide may be used in renal failure, but monitoring of acid-base balance is recommended. Dosage and frequency of administration of other sulfonamides must be adjusted in renal failure based on serum levels. No data is available on dosing in hepatic insufficiency.

SIDE EFFECTS/TOXICITY

Allergic reactions with rash and itching are relatively common. Nausea, vomiting, diarrhea, headache, and photosensitivity may occur. Rare but severe hypersensitivity reactions, including vasculitis, anaphylaxis, serum sickness, and Stevens-Johnson syndrome, may occur [131]. Sulfacetamide lotion also contains metabisulfite, which may cause an allergic reaction in patients allergic to sulfites [6].

Sulfonamide ophthalmic preparations may cause local irritation. The topical mafenide may cause pain or burning locally. Systemic reactions may develop during treatment with ophthalmic and topical preparations of sulfonamides due to systemic absorption.

Less common reactions include metabolic acidosis that may occur with absorption of mafenide due to a byproduct, (rho) carboxybenzenesulfonamide, that inhibits carbonic anhydrase. Very rare reactions with sulfonamides include blood dyscrasias (agranulocytosis, aplastic anemia, thrombocytopenia, hemolytic anemia), hepatitis and hepatocellular necrosis, and toxic nephrosis due to crystalluria. Hemolysis is more likely to develop in patients with G6PD deficiency [131].

Sulfonamides are contraindicated in patients who are known to be allergic to sulfa drugs and in cases where there have been previous adverse effects to sulfonamides [6].

DRUG INTERACTIONS

Warfarin, phenytoin, and sulfonylureas may all be potentiated due to displacement of the drugs from serum albumin by the sulfonamides [6]. Cyclosporine levels may be decreased, and levels should be monitored [6]. Administration of PABA may antagonize the effects of sulfa drugs.

SPECIAL POPULATIONS

Sulfa drugs should be avoided in pregnancy near term due to the increased potential for kernicterus in the newborn [131]. Animal studies with sulfamethoxazole show bone abnormalities and a higher incidence of cleft palate. Adequate studies have not been done in pregnant women [131].

Mafenide, sulfacetamide ophthalmic drops, and sulfadiazine are pregnancy category C. Sulfacetamide lotion has not been studied in pregnancy. Adverse events were not observed in animal reproduction studies of silver sulfadiazine; nevertheless, it is contraindicated for use near term in pregnant women [6].

Sulfonamides are excreted in breast milk. Sulfamethoxazole and sulfisoxazole are considered compatible with breastfeeding by the AAP, although they should be avoided if hyperbilirubinemia or G6PD deficiency is present [57]. Sulfacetamide lotion and silver sulfadiazine have not been studied in breastfeeding but would presumably also be excreted in breast milk; use with caution in breastfeeding women [6]. The manufacturer considers the use of sulfadiazine to be contraindicated in breastfeeding women [6].

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THE SULFONAMIDES					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Short- to Medium-Acting					
Sulfadiazine	2–4 g/day in 3 to 6 divided doses	>2 mos (initial): 75–150 mg/kg/day in 4 to 6 divided doses >2 mos (maintenance): 150 mg/kg/day in 4 to 6 divided doses Max: 6 g/day	PO	Rash, pruritus	Multiple drug interactions. Contraindicated in infants <2 mos of age.
Sulfamethoxazole/ trimethoprim (TMP/SMX)	PO: 1–2 DS tablets every 12 to 24 hrs IV: 8–20 mg TMP/kg/ day in 2 to 4 divided doses	>2 mos PO: 6–20 mg TMP/kg/day in 2 divided doses IV: 6–20 mg TMP/ kg/day every 12 to 24 hours Max single dose: 160 mg TMP/dose	PO, IV	Rash, pruritus	Multiple drug interactions. Weight-based dosing recommendations based on trimethoprim content.
Limited to GI Tract					
Sulfasalazine	RA: Initial: 0.5–1 g every 6 to 8 hrs Maintenance: 2 g/day in divided doses UC: Initial: 3–4 g in evenly divided doses every 8 hours Titrate to 4–6 g in 4 divided doses	>2 yrs: 40–60 mg/kg/ day in 3 to 6 divided doses	PO	Anorexia, headache, GI upset	Contraindicated with hypersensitivity to salicylates, sulfasalazine, sulfonamides, or mesalamine.
Topical					
Mafenide	Cream: Apply 1.6 mm thick layer to burn area every 12 or 24 hrs Solution: Wet dressing gauze every 4 hrs or as needed	Use adult dosing	Cream, powder for solution	Burning at application site, rash, allergic reaction	Used for treatment of second- and third-degree burns to prevent infection. Burn area should be covered with cream/wet at all times. Apply with sterile gloved hand.
Silver sulfadiazine	Apply 1.6-mm layer to burn area once or twice daily	Use adult dosing	Cream	Rash, allergic reaction	
Sulfacetamide	Dosage varies with the preparation.	Use adult dosing	Prepared in complex with other topical medications as a solution or ointment	Rash, local irritation	Combinations with fluoro-metholone, prednisolone, and phenylephrine are available, each with differ-ing dosing, indications, and contraindications. Common for ophthalmic and topical use.
Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications. DS = double strength; RA = rheumatoid arthritis; TMP = trimethoprim; UC = ulcerative colitis.					
Source: [6; 16]					*Table 7*

Because of the risk of neonatal kernicterus, use of sulfonamides should be avoided in the newborn. Sulfacetamide eye drops have not been studied in children younger than 2 months of age [6].

TETRACYCLINES

Chlortetracycline, the first tetracycline, was developed in 1948 as a product of *Streptomyces aureofaciens*. Chlortetracycline was altered to produce tetracycline. Doxycycline and minocycline are semisynthetic derivatives.

Tetracyclines bind to the 30S ribosomal subunit (and possibly the 50S ribosomal subunits of susceptible bacteria), blocking the binding of aminoacyl transfer-RNA [6; 138]. This results in inhibition of protein synthesis, with bacteriostatic effects.

Bacterial resistance is typically the result of mutations that either prevent entrance of tetracyclines into the cell or increase the export of tetracycline out of the cell [139]. The resistance may be transmitted by plasmids [140].

MECHANISMS OF ACTION AND PHARMACOKINETICS

The tetracyclines have a broad spectrum of activity that includes aerobic gram-positive and gram-negative bacilli, atypical bacteria (such as *Chlamydia trachomatis*, *Chlamydia psittaci*, and *Mycoplasma pneumoniae*), and spirochetes (such as *Borrelia burgdorferi*). Tetracycline is also a second-line agent for *T. pallidum*. It is approved by the FDA for treatment of rickettsial infections, typhus, Rocky Mountain spotted fever, trachoma, nongonococcal urethritis, and lymphogranuloma venereum [6].

As a result of decades of clinical and agricultural use, the prevalence of resistance to tetracyclines is now high among common gram-positive and gram-negative pathogens. For this reason, and because they are bacteriostatic, the role of tetracyclines is limited for treatment of most pyogenic infections. Primary indications for this class are atypical infections (e.g. mycoplasma and chlamydia) and zoonoses (e.g. tularemia and brucellosis).

The tetracyclines may be divided into three groups based on their pharmacokinetic traits. These groups are the short-acting group, intermediate-acting group, and long-acting group. The varying half-lives are the result of different rates of renal excretion [6].

Short-Acting Tetracyclines

The short-acting tetracyclines include tetracycline, the namesake of the class. Frequent dosing is needed because of the very short half-life of these agents. The class previously included oxytetracycline, but the agent is no longer available in the United States [6]. Tetracycline is inexpensive but requires dosing every six hours for most indications. A less frequent dosage protocol is commonly used for the treatment and prevention of acne [6].

Intermediate-Acting Tetracyclines

The only intermediate-acting agent available in the United States is demeclocycline. Demeclocycline is no longer used as an antibiotic but rather has been used as an off-label drug to treat the syndrome of inappropriate antidiuretic hormone (SIADH) [6; 141]. However, studies have suggested that there is limited high-quality evidence to suggest that demeclocycline is effective in managing this condition, and European clinical practice guidelines recommend against the use of demeclocycline for the management of hyponatremia in patients with SIADH [6; 142].

Long-Acting Tetracyclines

The long-acting tetracycline agents include doxycycline and minocycline. The main difference between these and the short-acting agents is that these may be dosed less frequently (once or twice daily), which is an advantage in ensuring compliance [6]. The spectrum of bacterial coverage is essentially the same and the indications are the same, with the additional indication for the treatment of inhalation anthrax as part of a multidrug regimen.

ABSORPTION/ELIMINATION

Tetracycline is well absorbed after an oral dose taken in the fasting state. Doxycycline and minocycline are well absorbed after an oral dose and may be given with or without food.

The tetracyclines are well distributed throughout body tissues and fluids; distribution in the CSF is adequate for the treatment of some infections [6; 143; 144]. The excellent tissue penetration results in the ability of the drug to cross into the dentin, where the tetracycline permanently chelates with the calcium [145].

Most of the tetracycline dose is excreted unchanged into the urine by glomerular filtration, although there is some biliary excretion as well. Nonrenal, possibly hepatic, mechanisms account in large part for excretion of doxycycline and minocycline. Approximately 23% to 40% of doxycycline and 5% to 12% of minocycline is excreted in the urine [6].

Tetracycline should be used with caution in the presence of renal insufficiency, because it accumulates rapidly in the serum in the presence of decreased renal function [6]. Doxycycline may be used in renal failure, as it will be excreted into the bile [6; 146]. Hepatotoxicity has been rarely reported [6].

SIDE EFFECTS/TOXICITY

Tetracyclines commonly cause GI upset, including nausea, vomiting, and diarrhea. There is conflicting evidence of staining and deformity of the teeth in children younger than 8 years of age. Photosensitivity, idiopathic intracranial hypertension, esophageal ulceration, and hepatotoxicity occur rarely [6].

Minocycline is often associated with vertigo, nausea, and vomiting, and it may increase azotemia in renal failure. In addition, prolonged use of minocycline may cause reversible discoloration of the fingernails, the sclera, and the skin [6]. Minocycline has been associated with a lupus-like reaction [6].

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THE TETRACYCLINES					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range[a]**	**Route**	**Common Side Effects**	**Comments**
Short-Acting					
Tetracycline	250–500 mg every 6 to 12 hrs	25–50 mg/kg/day in 4 divided doses	PO	Photosensitivity, tooth enamel deformities in children <8 yrs of age	Polyvalent cations decrease absorption.
Intermediate-Acting					
Demeclocycline	150 mg every 6 hrs or 300 mg every 12 hrs	≥8 years: 8–12 mg/kg/day in 2 to 4 divided doses	PO	GI upset, tooth enamel deformities in children <8 yrs of age	Polyvalent cations decrease absorption. Use caution if used with warfarin.
Long-Acting					
Doxycycline	PO: 100–200 mg/day in 1 to 2 divided doses IV: 100 mg every 12 hrs	<45 kg: 2–5 mg/kg/day in 1 to 2 divided doses Max: 200 mg/day >45 mg: Same as adult dosing	PO, IV	Phlebitis at IV site, photosensitivity, tooth enamel deformities in children <8 yrs of age	Polyvalent cations decrease absorption. Use caution if used with warfarin.
Minocycline	Initial: (IV, PO): 200 mg Maintenance: (IV): 100 mg every 12 hrs Max: 400 mg/day Maintenance (PO): 100 mg every 12 hrs, OR 100–200 mg initially, followed by 50 mg 4 times daily	Initial: (IV, PO): 4 mg/kg/dose Maintenance: 2 mg/kg/dose every 12 hrs Max: 400 mg/day	PO, IV	GI upset, tooth enamel deformities in children <8 yrs of age	
Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications. SIADH: syndrome of inappropriate antidiuretic hormone hypersecretion. [a]All pediatric doses are for children older than 8 years of age.					
Source: [6; 16]					*Table 8*

Allergic reactions to tetracyclines are not common but may range from mild rashes to anaphylaxis. Tetracyclines are contraindicated in patients who have shown hypersensitivity to any tetracyclines.

DRUG INTERACTIONS

Several types of drug interactions result in alterations in serum levels of tetracyclines. Agents that alkalinize the urine will increase excretion of the tetracyclines. Polyvalent metal cations (calcium, aluminum, zinc, magnesium, and iron) and bismuth decrease absorption [6; 147]. Drugs that induce hepatic enzymes may decrease the half-life of doxycycline.

Interactions that affect the efficacy of other drugs also occur. The bactericidal effect of penicillins may be decreased by co-administration with tetracyclines. Concurrent use of oral contraceptives may make the contraceptive less effective [6; 148; 149]. The effects of warfarin are increased, probably because tetracyclines depress warfarin metabolism and plasma prothrombin activity, resulting in a synergistic effect [6; 150]. Digoxin effects may be increased because of changes in the bowel flora that are responsible for digoxin metabolism [151].

SPECIAL POPULATIONS

Tetracycline is pregnancy category D because of impaired bone development in the fetus. Hypoplasia of the enamel and discoloration of fetal teeth may occur, and maternal hepatic toxicity has been reported as well [6; 152; 153].

Tetracyclines are excreted into the breast milk in small amounts. Most exposed infants have very low blood levels of the drug and probably are not at risk [6]. In the past, tetracyclines were contraindicated in children younger than 8 years of age because of the risk for tooth deformity. However, doxycycline is the current first-line therapy for Rocky Mountain spotted fever in children of all ages, including those younger than 8 years of age [154]. Limited studies indicate that short courses of the medication were not associated with dental side effects in this population [155].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Infectious Diseases Society of America asserts that tetracyclines should not be used in children younger than 8 years of age.

(https://academic.oup.com/cid/article/52/3/e18/306145. Last accessed January 11, 2024.)

Level of Evidence: A-II (Good evidence from >1 well-designed clinical trial, without randomization; cohort or case-controlled analytic studies; multiple time-series; or dramatic results from uncontrolled experiments)

VANCOMYCIN

Vancomycin is the oldest member of the glycopeptide antibiotics class, a group of large molecules that inhibit bacterial cell wall synthesis. Glycopeptides have a high binding affinity for peptides found only in bacterial cell walls. This interaction disrupts peptidoglycan polymerization, the late-stage reaction that imparts rigidity to the cell wall [6; 156]. Gram-positive organisms, both cocci and bacilli, are highly susceptible to glycopeptides.

Vancomycin was developed more than 50 years ago as an alternative intravenous therapy for serious staphylococcal and streptococcal infections in patients allergic to beta-lactams. In this early period, vancomycin usage was associated with a high incidence of vestibular and renal toxicity. The cause was attributed in large part to impurities in the formulation, a problem solved in subsequent years. At present, the major role for vancomycin is in the treatment of serious infections caused by MRSA, methicillin-resistant *S. epidermidis* (MRSE), and ampicillin-resistant enterococci [157]. An oral formulation is available for the treatment of *C. difficile*-associated diarrhea/colitis.

MECHANISMS OF ACTION AND PHARMACOKINETICS

Vancomycin is not absorbed by the intestinal tract and must be administered by intravenous infusion, except for the formulation for the treatment of *C. difficile*-associated diarrhea/colitis [6]. The determination of a safe, effective dosage regimen, and decisions regarding monitoring of therapy, are complex matters that require consideration of multiple factors, including the site and severity of infection, the patient's weight and renal function, the susceptibility of the infecting organism, and the anticipated duration of therapy [158]. The usual adult dose is 15–20 mg/kg/dose every 12 hours. The rate of infusion should be no more than 500 mg/hour, as rapid infusion causes an uncomfortable generalized erythroderma ("red man" syndrome) [6]. The red man syndrome is a histamine-mediated flushing that occurs during or immediately following infusion and does not mandate discontinuation unless slowing the infusion rate fails to mitigate the reaction.

ABSORPTION/ELIMINATION

Vancomycin is cleared almost entirely by the kidneys. Prolonged usage at excessively high therapeutic serum levels has been associated with nephrotoxicity and ototoxicity [6]. In treating patients with invasive staphylococcal infection and MRSA, it is considered important to use the maximum dosage (target trough serum vancomycin level of 15–20 mcg/mL) in order to assure optimal therapeutic effect [158]. The serum creatinine and trough vancomycin level (target <20 mcg/mL) should be monitored once or twice weekly in such cases, as well as in all patients who are elderly or have impaired renal function.

SIDE EFFECTS/TOXICITY

Apart from the (avoidable) red man syndrome, vancomycin administration is well tolerated and side effects are uncommon. As with beta-lactams and sulfonamides, vancomycin is a good sensitizing agent; allergic manifestations such as fixed drug eruptions and drug fever are relatively common. Vancomycin nephrotoxicity does occur. The incidence is low, the exact mechanism is poorly understood, and the impact is usually reversible upon discontinuation of the drug. Risk factors for nephrotoxicity include total daily dose in excess of 3–4 grams, trough serum vancomycin levels >20 mcg/mL, pre-existing renal disease, concomitant use of other nephrotoxic drugs (e.g. aminoglycosides), and duration of therapy longer than one week [159].

In 2017, the FDA published a safety review that indicated that use of intraocular vancomycin prophylactically during cataract surgery, alone or in a compound formula, should be avoided because of the risk of hemorrhagic occlusive retinal vasculitis [6; 160].

Reversible neutropenia, presumably from bone marrow toxicity, is sometimes seen in patients receiving prolonged vancomycin therapy (e.g., for endocarditis and osteomyelitis). Oral vancomycin is not absorbed and thus imposes no risk of nephrotoxicity or ototoxicity.

ANTIMICROBIAL PEPTIDES

The increasing prevalence of antimicrobial resistance among clinical isolates of staphylococci and streptococci severely limits therapeutics for serious infections caused by these common pathogens. Thus, there is ongoing research on alternative antimicrobial mechanisms and development of novel therapies needed for treatment of multidrug-resistant bacterial infection. Antimicrobial peptides are naturally occurring molecules and semisynthetic derivatives that have bactericidal activity against micro-organisms. Naturally occurring peptides with antimicrobial activity are produced by a variety of organisms (e.g., plants, insects, marine life) and serve to protect the host from pathogenic micro-organisms. Antimicrobial peptides exert their effects via multiple mechanisms: cell-membrane attachment, disruption, and leakage of cell contents; inhibition of

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intracellular protein and nucleic acid synthesis; attenuation of protein folding; and prevention of cell wall biosynthesis [175].

DAPTOMYCIN

Daptomycin is a cyclic lipopeptide produced by Streptomyces roseosporus having bactericidal activity against a wide range of gram-positive cocci. The spectrum of activity includes human pathogens such as methicillin-sensitive Staphylococcus aureus, MRSA, and Enterococcus. The exact mechanism of action is unclear; it targets the bacterial cell membrane where interactions lead to rapid depolarization due to potassium efflux, leakage of cell contents, and disruption of the architecture of the cell membrane [175]. Following clinical trials to assess efficacy and the parameters of safe dosage, daptomycin was approved by the FDA in 2006 for parenteral treatment (4 mg once daily) of complicated bacterial skin and soft tissue infections. Subsequent experience and formal clinical trials have demonstrated that daptomycin efficacy is comparable to standard therapy for treatment of MRSA bacteremia and endocarditis, especially when administered at the higher dose of 6–10 mg daily. Daptomycin is an option for salvage and first-line treatment of bacteremia, endocarditis, and osteomyelitis caused by MRSA and Enterococcus isolates showing resistance to vancomycin (minimal inhibitory concentration >2 mg/L) [176].

Adverse effects of daptomycin are rare with once daily dosing. Skeletal myopathy has been reported, mostly prior to 2006 when daptomycin was administered in multiple daily doses. When high dosage or prolonged daptomycin regimens are employed, coadministration with other drugs associated with myopathy, such as hydroxymethylglutaryl CoA reductase inhibitors (statins), should be avoided, and patients should be monitored for muscle pain or weakness [177]. Eosinophilic pneumonia has been reported in association with prolonged treatment of osteomyelitis. In a cohort study involving 1,021 patients who received daptomycin for bone and joint infections, 17 (1.7%) were diagnosed with daptomycin-induced eosinophilic pneumonia [178]. All patients recovered upon discontinuation of daptomycin.

LYPOGLYCOPEPTIDES

Lipoglycopeptides are semisynthetic derivatives of glycopeptides, akin to vancomycin and developed for treatment of multidrug-resistant staphylococcal and enterococcal infections. These newer agents have enhanced activity and favorable pharmacokinetics—in some cases, permitting administered at weekly intervals. In comparison to vancomycin, lipoglycopeptides have greater potency against gram-positive bacteria, including vancomycin-resistant strains, and appear less likely to lead to emergence of resistant organisms [161; 162; 179]. As with vancomycin, lipoglycopeptides must be administered intravenously. The lipophilic side chain prolongs plasma half-life and helps anchor these agents to the outer structure of the bacterial cell, inhibiting cell wall synthesis and disrupting cell membrane integrity [163]. In animal studies, lipoglycopeptides have proven effective in treating a variety of serious gram-positive infections, including bacteremia, pneumonia, and endocarditis [161; 162]. Clinical studies of efficacy in humans have been limited to date.

At present, three lipoglycopeptides, telavancin, dalbavancin, and oritavancin, are approved by the FDA for the treatment of acute bacterial skin and soft-tissue infection. Clinical trials show equivalent or superior efficacy against MRSA skin infection when compared with vancomycin [7; 162; 164]. Telavancin is also approved for treatment of hospital-acquired and ventilator-associated *S. aureus* pneumonia. A phase III clinical trial is ongoing to assess telavancin efficacy and safety for treatment of complicated *S. aureus* bacteremia and right-sided endocarditis [179]. The side effect profile of these agents is mild and comparable to other effective regimens. Reported adverse effects include headache, nausea, pruritus, pain at injection site, and fever. Taste disturbance (i.e., metallic taste), nausea and vomiting, and foamy urine have been reported with telavancin [6; 163].

Of note, a risk/benefit analysis should be conducted when using telavancin in patients with pre-existing moderate-to-severe renal impairment treated for hospital-acquired or ventilator-associated bacterial pneumonia, as mortality is increased compared with administration of vancomycin [6].

Dalbavancin has the advantage of a prolonged plasma half-life (6 to 10 days), allowing for weekly administration and perhaps obviating the need for an indwelling central line. In adults and children 12 to 17 years of age, the best-studied treatment protocol is 1 g IV, followed by 500 mg weekly [164; 165]. In a randomized trial comparing dalbavancin (1 g IV on days 1 and 8) with vancomycin (IV for 3 days followed by the option of oral linezolid to complete 10 to 14 days) for treatment of skin infection, the clinical response outcomes were similar in both treatment arms. For patients with *S. aureus* infection, including MRSA, clinical success was observed in 90.6% of patients treated with dalbavancin and 93.8% of those who received vancomycin-linezolid [164].

The lipoglycopeptides have had some adverse effects on fetal development in animals; safety data in pregnant women are limited. These agents should be used during pregnancy only when the benefit outweighs the risk [163].

PLEUROMUTILINS

Pleuromutilins were discovered as natural-product antibiotics in 1950. However, their use was limited to veterinary medicine until 2007, when the first agent (retapamulin) was approved for use in humans [166]. Retapamulin was only approved for topical application. In 2019, lefamulin was approved for human use via oral and intravenous delivery [6]. Pleuromutilin derivatives are designed primarily through modifications at the C(14) side chain [166].

These agents inhibit bacterial protein synthesis through interactions (hydrogen bonds, hydrophobic interactions, and Van der Waals forces) with the A- and P-sites of the peptidyl transferase center in domain V of the 23s ribosomal RNA of the 50S subunit [6]. The binding pocket of the bacterial ribosome closes around the mutilin core for an induced fit that prevents correct positioning of transfer RNA [6].

Retapamulin is used for the topical treatment of impetigo. A small amount is applied to the affected area twice per day for five days [6]. Possible side effects include eczema, application site reactions, diarrhea, headache, and nasopharyngitis.

Lefamulin is approved for the treatment of community-acquired bacterial pneumonia [6; 167]. The usual dose is 600 mg every 12 hours for oral administration or 150 mg every 12 hours for IV use [6]. Treatment is generally at least five days; patients should be afebrile for ≥48 hours and clinically stable prior to discontinuation. The most common adverse reactions include diarrhea, nausea, injection site reactions, elevated liver enzymes, and vomiting [167]. It is contraindicated in patients with certain arrhythmias or who are prescribed drugs to prolong QT intervals.

INVESTIGATIONAL ANTIBIOTICS FOR DRUG-RESISTANT MICRO-ORGANISMS

Researchers continue to explore new methods and the search for drugs to aid in the prevention of antibiotic resistance. Progress has been made in recent years, with two new antibiotics void of cross-resistance with existing antibiotics being discovered through soil sample screening: teixobactin and pseudouridimycin.

Teixobactin, a cyclic depsipeptide antibiotic, works by binding to a highly conserved motif of lipid II (precursor of peptidoglycan) and lipid III (precursor of cell wall teichoic acid), inhibiting bacterial cell wall biosynthesis [168; 169]. Teixobactin has been shown effective at treating an array of gram-positive pathogens, including MRSA, vancomycin-resistant *Enterococcus*, and *Mycobacterium tuberculosis*, with no known cross-resistance to other antibiotics [168; 169]. With reports in 2016 of efficient syntheses of two teixobactin analogues, this class of drugs may be part of the solution to bacteria resistant to currently available antibiotics [168; 169].

Pseudouridimycin, a nucleoside-analog inhibitor, acts by inhibiting bacterial RNA polymerase, an enzyme responsible for bacterial RNA synthesis, through a binding site. The structure is similar to rifampin, an antitubercular agent that inhibits the enzyme; however, the mechanism of action does differ so as not to cause a cross-reaction with rifampin [170; 171]. Pseudouridimycin has been shown effective for a broad spectrum of drug-sensitive and drug-resistant bacteria.

Researchers are currently attempting to conduct synthesis of these two new classes of drugs with varying, but promising, success. Although it may take several years for these or other new antibiotics with no cross-resistance to be developed, promising progress is continuing, and researchers estimate that, once approved, resistance to these novel drugs could take decades, rather than years, to develop [168; 169; 170; 171].

CONCLUSION

Antibiotics are commonly used drugs that have diverse actions, side effects, and toxicities. The large number of antibiotics available makes it challenging to understand the important characteristics of each antimicrobial class, including clinical indications, spectrum of activity, dosage, and toxicities. Knowing the general characteristics by antibiotic class and having experience with one or two key agents within each class improves recall and facilitates the selection of the most appropriate antibiotic for a given bacterial infection.

An understanding of the mode of action, spectrum of activity, and potential toxicity enables the practitioner to tailor a therapeutic regimen specific to the infectious etiology and of appropriate duration. This in turn lessens the likelihood developing microbial resistances and reduces risk of adverse effects.

It is important to remember that the indications given by the FDA are guidelines. Many antibiotics are used for off-label purposes, and occasionally in doses that differ from those recommended for the usual indications. This may be necessary when faced with managing severe and life-threatening infections or for special populations, such as premature infants, neonates, and the elderly. Before using a specific agent, one should always consider carefully reviewing the detailed information (package insert) provided by the manufacturer.

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COURSE TEST - #95074 ANTIBIOTICS REVIEW

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 January 31, 2027.

1. Which of the following classes of antibiotics is associated with a risk for developing *Clostridioides difficile*-associated diarrhea?
- A) *Macrolides*
- B) *Quinolones*
- C) *Cephalosporins*
- D) *All of the above*

2. Bacteria become resistant to the effects of antibiotics by
- A) *altered cellular permeability.*
- B) *increased efflux of the antibiotic from the cell.*
- C) *elaboration of deactivating enzymes that alter interactions at binding sites.*
- D) *All of the above*

3. Which of the following are common ways for bacteria to gain antibiotic resistance?
- A) *Genetic mutations*
- B) *Transfer of genetic information on plasmids*
- C) *Both A and B*
- D) *None of the above*

4. The first oxazolidinone created, which was developed in an attempt to stay ahead of the developing bacteria resistance, was
- A) *linezolid.*
- B) *cefprozil.*
- C) *norfloxacin.*
- D) *meropenem.*

5. What recommendation has the CDC made regarding infection control to minimize the spread of antibiotic resistances among patients in hospitals and residential care facilities?
- A) *Tailor treatment plans to the most likely pathogens*
- B) *Proper hand washing during and after patient care and implementation of hospital infection control programs*
- C) *Proper use of invasive medical devices only when they are necessary*
- D) *All of the above*

6. The antibacterial effect of penicillins is caused by the drugs' action of
- A) *inhibiting protein synthesis.*
- B) *impairing cell wall synthesis.*
- C) *blocking the binding of aminoacyl transfer-RNA.*
- D) *displacing cations that link phospholipids together.*

7. Labeled uses for the natural penicillins include treatment of infections of the
- A) *eye.*
- B) *meninges.*
- C) *gastrointestinal tract.*
- D) *upper and lower respiratory tracts.*

8. Which of the following is an absolute contraindication for administering penicillins?
- A) *Severe renal failure*
- B) *Severe hepatic failure*
- C) *Prior allergic reaction to a member of the class*
- D) *All of the above*

9. Which of the following is considered a first-generation cephalosporin?
- A) *Cefixime*
- B) *Cefepime*
- C) *Cefadroxil*
- D) *Loracarbef*

10. What route of elimination is used by members of the cephalosporin class of antibiotics?
- A) *Renal*
- B) *Mixed renal/hepatic*
- C) *Hepatic metabolism with excretion into the bile*
- D) *All of the above*

11. Probenecid increases serum levels of which cephalosporin?
- A) *Cefotetan*
- B) *Cefotaxime*
- C) *Ceftriaxone*
- D) *All of the above*

Test questions continue on next page →

12. Meropenem is approved by the FDA for the treatment of
- A) *pneumonia.*
- B) *urinary tract infections.*
- C) *intra-abdominal infections.*
- D) *meningitis in patients younger than 3 months of age.*

13. One side effect associated with the use of imipenem/cilastatin is
- A) *diarrhea.*
- B) *headache.*
- C) *hypotension.*
- D) *phlebitis at the infusion site.*

14. Aztreonam is considered pregnancy category
- A) *A.*
- B) *B.*
- C) *C.*
- D) *D.*

15. Aminoglycosides are effective for the treatment of
- A) *anaerobic bacilli.*
- B) *gram-positive bacilli.*
- C) *aerobic gram-negative bacilli.*
- D) *All of the above*

16. Which of the following aminoglycosides is taken orally as a bowel decontaminant due to its minimal absorption?
- A) *Neomycin*
- B) *Gentamicin*
- C) *Tobramycin*
- D) *Streptomycin*

17. Which of the following is a well-established side effect of the aminoglycosides?
- A) *Ototoxicity*
- B) *Nephrotoxicity*
- C) *Both A and B*
- D) *None of the above*

18. Which of the following is a topical sulfonamide?
- A) *Sulfadiazine*
- B) *Sulfasalazine*
- C) *Sulfacetamide*
- D) *Sulfadoxine/pyrimethamine*

19. Of the tetracyclines, which drug is mainly excreted in the urine?
- A) *Tetracycline*
- B) *Minocycline*
- C) *Doxycycline*
- D) *All of the above*

20. Which of the following is a contraindication for administering tetracycline?
- A) *Age older than 65 years*
- B) *Age younger than 8 years*
- C) *Patient history of syndrome of inappropriate antidiuretic hormone secretion*
- D) *Both A and B*

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Hyperlipidemias and Atherosclerotic Cardiovascular Disease

Audience
This course is designed for pharmacists and other healthcare professionals 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 at NetCE.com.)

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

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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 preventing 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].

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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*

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 eliminate 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%.

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.

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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*

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].

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

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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 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].

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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*

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].

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].

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., obe-

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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*

sity, 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.

EVIDENCE-BASED PRACTICE RECOMMENDATION

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.

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

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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].

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*

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 treatments" [152]. Analysis of the risk-benefit ratio of statins

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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].

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].

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*

EVIDENCE-BASED PRACTICE RECOMMENDATION

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].

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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]. How-

ever, 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.

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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 effectively 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

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*

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 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.

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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*

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 risk or borderline 10-year ASCVD risk, if risk-based decisions for preventive therapy such as statin treatment remain uncer-

tain, 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].

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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%
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 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.

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.

RESOURCES

The following resources are provided for those clinicians in need of additional information or as patient education sources.

American Heart Association (AHA)
https://www.heart.org

Professional Heart Daily
(A service provided by the AHA)
https://professional.heart.org

My Life Check: Life's Essential 8
https://www.heart.org/en/healthy-living/healthy-lifestyle/lifes-essential-8

Heart and Stroke Foundation of Canada
https://www.heartandstroke.ca

Centers for Disease Control and Prevention Cholesterol Homepage
https://www.cdc.gov/cholesterol

National Center for Health Statistics
https://www.cdc.gov/nchs

National Heart, Lung, and Blood Institute
https://www.nhlbi.nih.gov

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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*

Test questions continue on next page ➞

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*

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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.

Prescription Opioids: Risk Management and Strategies for Safe Use

Audience

This course is designed for pharmacists and other healthcare professionals involved in the care of patients prescribed opioids to treat pain.

Course Objective

The purpose of this course is to provide the information necessary for clinicians to make informed decisions regarding prescribed opioids in order to minimize adverse events, substance abuse, and drug diversion.

Learning Objectives

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

1. Define terms associated with opioid therapy and aberrant drug use.
2. Analyze behavioral responses to prescribed opioids and signs of emerging opioid misuse.
3. Outline the impact of clinical and professional society attitudes toward opioid prescribing.
4. Review the role of OxyContin in the rise of prescribed opioids for chronic noncancer pain.
5. Evaluate the basic epidemiology of prescription opioid use, misuse, and dependence in the United States.
6. Identify factors that influence opioid prescribing decisions.
7. Describe the morbidity and mortality associated with the use of prescription opioids.
8. Discuss characteristics of appropriate and inappropriate opioid prescribing and contributory factors to both.
9. Compare opioid abuse risk assessment tools and the utility of risk stratification.
10. Outline the appropriate periodic review and monitoring of patients prescribed opioid analgesics, including the role of urine drug testing.
11. Describe necessary components of patient/caregiver education for prescribed opioid analgesics, including guidance on the safe use and disposal of medications.
12. Compare available opioid abuse-deterrent formulations.
13. Evaluate government and industry efforts to address problems arising from prescription opioid analgesic misuse.
14. Review the unintended negative consequences of efforts to reduce prescribed opioid analgesic misuse, diversion, and overdose.
15. Discuss treatment considerations for patients with active or remitted substance use disorder who require prescribed opioid analgesics for chronic pain.

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.

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Faculty Disclosure

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

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INTRODUCTION

In the United States, the use of prescription opioids for the treatment of pain is challenging and complex. There exists a prevailing tendency to inappropriate patterns of underprescribing (because of fear of adverse effects and addiction) or overprescribing (because of failure to select properly or frustration over a poor therapeutic response). These practice patterns are especially prevalent in the management of patients with chronic noncancer pain and have resulted in or contributed to unnecessary patient suffering from inadequately treated pain and increasing rates of opioid abuse, addiction, diversion, and overdose.

Morphine was synthesized close to 200 years ago and entered clinical use more than 150 years ago. To this day, morphine and its opioid analogs remain the most powerful analgesics for severe acute pain and effective therapies for many chronic pain conditions. Opioid analgesic prescribing for pain control has risen dramatically since the late 1990s, and although opioid analgesic use in moderate-to-severe acute pain, cancer pain, and terminal pain is widely accepted, its use in chronic noncancer pain remains controversial [1]. Opioids can provide effective pain control, but problematic side effects are common, long-term outcomes vary, and escalating rates of addiction, diversion, and fatal overdose involving opioids have occurred in tandem with their increasing clinical use for pain control. These negative outcomes from increasingly

widespread prescribing have heightened awareness of the need for prescribers to mitigate the inherent risks that come with opioid analgesics in order to minimize their abuse, addiction, diversion, and fatal toxicity [2].

There is a shortage of pain specialist physicians in the United States that is expected to worsen, and this has resulted in most of the medical care for patients with chronic pain being delivered by primary care physicians [3]. The current problems involving prescription opioid analgesics are primarily the result of prescriber factors and the undue influence of stakeholders over pain medicine practice [4; 5]. Prescriber factors include inappropriate opioid prescribing and inadequate patient counseling and monitoring, reflecting deficits in knowledge, competence, and performance [6]. Many primary care providers lack sufficient knowledge or training in pain medicine and in appropriate opioid use, and the majority report they do not feel confident managing chronic pain [7; 8]. A clinical skills assessment by the American Academy of Family Physicians found significant and widespread knowledge deficits among family practice physicians in the medical skills necessary for providing optimal pain management, managing drug abuse and addiction, and utilizing risk evaluation and mitigation strategies when prescribing opioids [9].

The goal of this course is provide clinicians with an understanding of the essential components of appropriate opioid prescribing. This objective will be achieved through discussion of behavioral responses in patients receiving opioids for pain; the antecedents, catalysts, manifestations, and consequences of the dramatic and widespread increase in clinical and illicit use of prescription opioids; the assessment and management of pain; patient risk of developing problems with their prescribed opioid analgesic; governmental, law enforcement, and industry strategies and tactics to reduce prescription opioid abuse; and treatment approaches for patients with comorbid chronic pain and substance use disorders. Among primary care providers, there is great variability in the understanding of opioid use and misuse and in the confidence with which opioids are used for management of chronic pain. Often, there is confusion or difficulty distinguishing physiological tolerance and dependence or uncontrolled pain behaviors from symptoms and signs of opioid use disorder. In addition to substantial differences in patient tolerability and analgesia with opioid analgesics, patients can also exhibit a range of psychological, emotional, and behavioral responses to prescribed opioids, the result of inadequate pain control, an emerging opioid use problem, or both. An appreciation for the complexities of opioid prescribing, and the dual risks of litigation due to inadequate pain control and drug diversion or misuse, is necessary for all clinicians in order to provide the best possible patient care and to prevent a growing social problem.

There is also considerable evidence that, in the past, major stakeholders have negatively influenced the delivery of safe, effective, and appropriate analgesic care to patients with chronic pain. This has occurred, in part, through bias of the information provided to clinicians to guide their practice and prescribing behavior with respect to opioid analgesics. Effective practice is based on training, clinical judgment, and ongoing study of advances in practice areas. Careful clinicians pay attention to published research and other mediums of knowledge transfer that are relevant to their particular practice, with a trained eye toward the quality of evidence. Unfortunately, much of what has been published on chronic pain management, especially as regards opioid drug use, has uncertain validity because of various forms of bias and nonrigorous statistical analysis. This has had an adverse impact on the consistency and quality of care, on clinician confidence in how to render care, and on the public health cost of opioid analgesic care. For these reasons, an ***Appendix*** to this course has been included to provide some historical perspective on opioid prescribing practices and to address sources of bias in clinical (therapeutic) research.

DEFINITIONS

Definitions and use of terms describing opioid analgesic misuse, abuse, and addiction have changed over time, and their current correct use is inconsistent not only among healthcare providers, but also among federal agencies reporting epidemiological data such as prevalence of opioid analgesic misuse, abuse, or addiction. Misuse and misunderstanding of these concepts and their correct definitions has resulted in misinformation and represents an impediment to proper patient care.

OPIOID ABUSE, DEPENDENCE, AND ADDICTION

Inappropriate opioid analgesic prescribing for pain is defined as the nonprescribing, inadequate prescribing, excessive prescribing, or continued prescribing despite evidence of ineffectiveness [10]. Appropriate opioid prescribing is essential to achieve pain control, to minimize societal harms from diversion, and to minimize patient risk of abuse, addiction, and fatal toxicity. The foundation of appropriate opioid prescribing is based on 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 [7]. A 2013 survey measured primary care physician understanding of opioids and addiction. Of the 200 participants, [11]:

- 35% admitted knowing little about opioid addiction.
- 66% and 57% viewed low levels of education and income, respectively, as causal or highly contributory to opioid addiction.
- 30% believed opioid addiction "is more of a psychological problem," akin to poor lifestyle choices rather than a chronic illness or disease.

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OPIOID USE TERMINOLOGY	
Term	**Definition**
Misuse, nonmedical use	Use of the opioid that departs from intended prescribing by the provider
Abuse	A maladaptive pattern of opioid use with the primary intent of achieving euphoria or getting high
Addiction	A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. Characterized by behavior including impaired control over drug use, compulsive drug use, continued use despite harm, and drug craving.
Physical dependence	The expected response to chronic administration of many drug classes such as opioids, anabolic steroids, and beta-blockers, manifesting in neurologic adaptation whereby a drug class-specific withdrawal syndrome is produced by abrupt cessation, rapid dose reduction, decreased blood concentration, or antagonist administration
Tolerance	A state of adaptation in which the physiologic changes from drug exposure over time lead to diminished drug effect
Pseudoaddiction	An iatrogenic condition whereby patients display aberrant drug-seeking behaviors mimicking opioid use disorder but driven by intense need for pain relief. Resolves with adequate pain relief.
Diversion	Transfer of a controlled substance from authorized to unauthorized possession or distribution
Opioid	Any compound that binds to an opioid receptor in the CNS, including naturally occurring, synthetic, and semi-synthetic opioid drugs and endogenous opioid peptides
Iatrogenic	A response, usually unfavorable, to a medical or surgical treatment induced by the treatment itself
CNS = central nervous system.	
Source: [10; 20; 21]	*Table 1*

- 92% associated prescription analgesics with opioid addiction, but only 69% associated heroin with opioid addiction.
- 43% regarded opioid dependence and addiction as synonymous.

This last point is very important because confusion and conflation of the clinical concepts of dependence and addiction has led to accusations of many nonaddicted patients with chronic pain misusing or abusing prescribed opioids and to failure to detect treatment-emergent opioid problems [12]. Knowledge gaps concerning opioid analgesics, addiction, and pain may be related to attitude gaps, and negative attitudes may interfere with appropriate prescribing of opioid analgesics. For example, when 248 primary care physician survey participants were questioned regarding their prescribing approach in patients with headache pain and either a past or current history of substance abuse, 16% and 42% of physicians, respectively, would not prescribe opioids under any circumstance [13]. Possibly contributing to this knowledge deficit is the extent of educational exposure to concepts central in pain management.

A 2018 systematic review evaluated pain medicine curricula in 383 medical schools in Australia, New Zealand, the United States, Canada, the United Kingdom, and Europe [14]. Pain medicine was primarily incorporated into anesthesia or pharmacology courses, rather than offered as a dedicated pain medicine module. Ninety-six percent of medical schools in the United Kingdom and the United States and nearly 80% of medical schools in Europe had no compulsory dedicated pain medicine education. The median number of hours of pain content in the entire medical school curriculum was 20 in Canada, 20 in Australia and New Zealand, 13 in the United Kingdom, 12 in Europe, and 11 in the United States [14].

The nomenclature related to addiction is often inconsistent, inaccurate, and confusing, partially reflecting the diverse perspectives of those working in the related fields of health care, law enforcement, regulatory agencies, and reimbursement/payer organizations. Changes over time in the fundamental understanding of addiction have also contributed to the persistent misuse of obsolete terminology [15]. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM), published by the American Psychiatric Association, is perhaps the most influential reference for the diagnosis of addiction and all other psychiatric disorders. Prior to the 2013 release of the DSM-5, previous versions eschewed the term "addiction" in favor of "substance dependence," with a separate diagnostic entity of "substance abuse" representing a lower-grade, less severe version of substance dependence [16]. Also in earlier DSM versions, physiological dependence, manifesting as substance tolerance and withdrawal, was considered a diagnostic criterion of substance dependence. The result was the perpetuation of patient and healthcare professional confusion between physical and psychological dependence and the belief that tolerance and withdrawal meant addiction. This confusion enhanced provider and patient fears over addiction developing from opioid analgesics and contributed to the undertreatment of pain [16]. The DSM-5 has eliminated the categories of substance dependence and substance abuse by combining them into the single diagnostic entity of substance use disorder. The disorder is measured on a continuum from mild to severe [16].

COMMON MISCONCEPTIONS OF PAIN THERAPY WITH OPIOID ANALGESICS AND ADDICTION	
Misconception or Belief	**Correction**
The tolerance and withdrawal of opioid dependence equates to opioid addiction.	Tolerance, withdrawal, and physiologic dependence are expected responses to opioids and other controlled substances when given in sufficient doses over time and are not, by themselves, indicative of addiction.
Addiction can be accurately predicted and diagnosed in the initial assessment of patients with pain.	Addiction is not an entirely predictable response to reward-producing drugs but may occur in biologically and psychologically susceptible individuals; it is diagnosed over time based on established criteria.
Medications for pain or anxiety should not be used in patients with a substance use disorder history.	Uncontrolled pain or anxiety and other psychiatric illnesses may trigger a relapse to substance use or exacerbate an existing disorder. Treatment should be tailored to patient need and may include alternative treatment modalities, monitored prescriptions, or other measures as needed.
Behaviors such as "clock-watching," preoccupation with obtaining opioid analgesics, deception, stockpiling unused medication, and illicit substance use indicate addiction.	Patients with undertreated pain may engage in problematic behaviors that mimic opioid abuse but are driven by intense need for relief and resolve with adequate pain control.
Substance misuse is the same as substance abuse, dependence, or addiction; all require cessation of opioid prescribing.	Many factors can underlie substance misuse, including varying cultural values, lack of education, misunderstandings, and poor judgment, that do not meet the criteria for a substance use disorder. Misuse does require evaluation for patient education and possible treatment modifications but does not mandate discontinuation of opioids.
Opioid therapy always leads to addiction.	This has been proven false; the rate of iatrogenic opioid use disorder is low.
Some opioids are worse than others in terms of addiction potential.	Addiction is the result of individual susceptibility, and any opioid analgesic can be abused by predisposed individuals.
If morphine is used now, there will not be options when the pain worsens.	An increase in pain severity can be countered by dose increase, switching to another opioid, or adding a non-opioid analgesic.
If I start taking an opioid, I will have to keep increasing the dose to control my pain.	After an effective dose is reached, many patients with chronic pain are able to maintain analgesia on the same dose.
Morphine and opioids cause heavy sedation and probably hasten death.	The initial sedation goes away within the first two weeks of initiation. Opioids have conclusively been shown to not hasten death in hospice patients; pain undertreatment is a far greater concern in hastening death.
Source: [15; 21]	*Table 2*

In 2011, the American Society of Addiction Medicine (ASAM) published their latest revision in defining the disease of addiction. Since that time, the public understanding and acceptance of addiction as a chronic brain disease and the possibility of remission and recovery have increased. Additionally, there is growing acknowledgment of the roles of prevention and harm reduction along the spectrum of addiction and recovery. Consequently, ASAM updated its definition of addiction and adopted the following revised definition in 2019 [17]:

> Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences. Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases.

According to the ASAM, the five characteristics of addiction are [18]:

- Inability to consistently abstain
- Impairment in behavioral control
- Craving or increased "hunger" for drug or reward experiences
- Diminished recognition of significant problems with one's behaviors and interpersonal relationships
- A dysfunctional emotional response

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TERMS TO AVOID OR LIMIT THE USE OF	
Term	**Rationale for not using**
Addicted/addiction	Frequently misused by those untrained to make the diagnosis. Not all who abuse are addicted.
Addictive	Patently false when describing a substance. Addiction resides within the person and not in the substance used. Some drugs do have high abuse liability, but most persons do not respond to exposure with addictive behavior.
Chemical coping	Overused in the literature and by clinicians. Not very helpful, especially if a better treatment or coping strategy is not immediately available.
Drug-seeking	Used when a patient is assumed to lack legitimate need for medication. Should be replaced with relief-seeking, if appropriate.
Hooked	Slang for addicted. Assumes the absence of medical need for the substance and suggests an off-hand, bad attitude.
Inebriated/intoxicated	A snap conclusion when a patient suspected of taking medication or other substance displays an altered sensorium. Better to objectively describe observations.
Malingering	Overcalled and best not expressed unless there is legally valid proof of deception for illicit purposes.
Narcotic	A term formerly referring to opium, morphine, and heroin and still used in the area of law and misused by media in reference to all opioids. Should never be used in a clinical or education context due to strong emotional association with crime, addiction, and death. Best replaced with opioid.
Painkiller	Negative use by media in reports of opioid addiction and overdose. Best replaced with pain reliever.
Source: [19]	*Table 3*

This summary of addiction should not be used as diagnostic criteria for addiction because the core symptoms vary substantially among addicted persons, with some features more prominent than others [17].

Many terms used in discussions of opioid use and misuse may have ambiguous meanings (***Table 1***). The absence of consensus in the terminology and definitions of substance use, substance use disorders, and addiction has led to considerable confusion and misconceptions (***Table 2***). These misconceptions may be harbored by clinicians, patients, family members, and the public and can negatively impact patient interaction, assessment, treatment, and outcomes. 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 (***Table 3***). Pejorative terminology has a strong negative effect on patients and serves to reinforce their sense of shame and stigma over using opioid analgesics. These terms signal a negative attitude and judgment to patients [15; 19].

BEHAVIORAL RESPONSES TO PRESCRIBED OPIOIDS

Patients with pain display a continuum of behavioral responses to prescribed opioids. Some develop aberrant behaviors, which are defined as unintended behaviors involving the acquisition or use of prescribed opioids [22]. Depending on the study, researchers have reported that as many as 40% of patients with pain receiving opioid therapy exhibit aberrant behavior; however, in only a minority of these patients does the aberrant behavior reflect an emerging opioid use disorder. It is important to distinguish the underlying basis and the level of risk for opioid use disorder represented in the aberrant behavior. This is accomplished by differential diagnosis (***Table 4***). To capture the perspective of pain practitioner viewpoints in associating aberrant behaviors and risk of patient opioid problems, 100 pain physicians were instructed to rank a list of 13 aberrant drug-use behaviors from least to most suggestive of emergent opioid use disorder. Selling the prescribed opioid and prescription forgery received highest ranking as most aberrant, and altered route of administration was given the third highest ranking. Lowest ranked were unkempt patient appearance, sporadic unsanctioned dose escalation, and prescribed opioid hoarding [23].

There are certain behaviors that are suggestive of an emerging opioid use disorder. The most suggestive behaviors are [24; 25; 26]:

- 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

CONSIDERATIONS FOR DIFFERENTIAL DIAGNOSES
• Inadequate pain management: – Stable condition but inadequate pain control – Progressive condition/pathology – Tolerance to opioids
• Inability to comply with treatment due to: – Cognitive impairment – Psychiatric condition
• Self-medication of mood, anxiety, sleep, post-traumatic stress disorder, etc.
• Diversion
Source: [19] *Table 4*

- 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 [23; 24; 25]:

- 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

It is essential for clinicians to consider poorly managed pain or poor coping skills as the basis for aberrant behavior. Even aberrant behaviors highly suggesting opioid abuse may reflect a patient's attempt to feel normal or alleviate emotional or physical distress. This is termed chemical coping and refers to the inappropriate use of a prescribed opioid to treat emotional or psychiatric conditions, commonly depression, anxiety, and insomnia. In these cases, the patient is not technically addicted to the opioid, but he or she fears withdrawal from the opioid and losing the ability to function without the drug and, as a result, may abuse opioids, engage in illegal behavior to obtain opioids, or doctor-shop. Aberrant behavior can also be driven by undertreated pain or a failure of treatment management [27]. Importantly, no single behavioral marker clearly identifies addiction in patients with pain who are prescribed opioids, and while all addicts are abusers, not all abusers are opioid-addicted [27].

For the purposes of this course, the term opioid addiction is used to indicate a severe opioid use problem, consistent with the definition of addiction provided earlier in this course and in place of the now-discarded DSM-IV term of opioid dependence. Opioid use disorder is used to encompass the range of problematic opioid use.

CLINICIAN AND PROFESSIONAL SOCIETY ATTITUDES TOWARD OPIOID PRESCRIPTION DRUG USE

BACKGROUND

Opium and its alkaloids have been used for thousands of years as analgesics. From the end of the 19th century into the early 20th century, heroin was sold as a cough suppressant and briefly promoted as more effective and less addictive than morphine. It was legally marketed in pill form and became widely abused for the intense euphoria by crushing the heroin pills into powder for inhalation or injection [1]. Heroin addiction skyrocketed, and Congress banned the drug in 1924. Wariness of prescribing opioids persisted through the 1980s and 1990s [28].

The United States has a long history of pain undertreatment as a standard medical practice. This was a consequence of the long-standing emphasis on treating the underlying primary illness, minimizing the importance of addressing pain, and viewing pain as an endurable consequence [1]. Another primary factor historically responsible for pain undertreatment has been a resistance to prescribing opioids, driven by fears of patient addiction and the threat of prosecution and potential loss of licensure if opioid prescribing was deemed inappropriate by the state medical board. The widespread practice of including non-professional lay members on medical boards intensified physician concerns over prejudicial interpretation by board members, even when legitimate medical necessity merited long-term, high-dose opioid prescribing to patients with severe, chronic noncancer pain [28].

These physician concerns were confirmed by the results of a 1992 survey that captured medical board member perception and opinion of legality and appropriateness in opioid prescribing for different pain conditions. A total of 304 members of 49 state medical boards were surveyed; 85% were physicians (MDs and DOs) and 15% were lay public members [29]. Physician members were asked to rank 12 opioids by their order of recommendation for chronic, moderate-to-severe cancer pain. The top selection was codeine with aspirin/acetaminophen (47%), despite codeine being widely accepted as too weak for chronic moderate-to-severe pain. When asked of the general incidence of psychological dependence (as compulsive non-medical use) from opioid pain treatment, 39% did not know.

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When asked to define "addiction" by selecting one or more of several common definitions, 85% chose physical dependence, 71% chose psychological dependence, 41% chose tolerance, 21% chose physical dependence alone, 10% chose psychological dependence alone, and 1% chose tolerance alone [29].

Respondents were also asked for their opinion, as state medical board members, of the legality and medical legitimacy of opioid prescribing longer than three months for several patient scenarios. Approximately 10% of board members described opioid prescribing as illegal under medical practice, controlled substances law, or both, and requiring investigation in patients with cancer pain alone, 26% in cancer pain with patient history of opioid abuse, 59% in chronic noncancer pain alone, and more than 90% in patients with chronic noncancer pain and history of opioid abuse [29]. Underscoring the gravity of these findings was that 80% of respondents stated their medical board was the agency most likely to investigate improper controlled substance prescribing in their state [29].

Against this backdrop, some pain physicians began to reexamine and challenge the intense physician reluctance to prescribe opioids. Observing the extent that suffering was relieved by opioids in cancer patients with severe pain and the apparent lack of euphoria that differed from the responses of opioid abusers, it was suggested that opioids could also be used to relieve suffering in many patients with intense, persistent noncancer pain, with little risk of addiction. This was followed by an effort to destigmatize the use of opioids, with the objective of easing access to opioids by the large number of patients with severe, persistent noncancer pain. While widely viewed as driven by good intentions, this crusade for acceptance of opioid use in noncancer pain was also accompanied by the regular tendency to minimize the inherent potential risks that accompany opioid prescription drug use, despite the absence of valid evidence to support the assumption [30].

Results from a 1986 chart review study of 38 patients with chronic noncancer pain receiving long-term opioid therapy were cited to support the assertion that long-term opioid use in patients with intractable nonmalignant pain was effective and safe with little risk of addiction. Of the 38 patients in the study, the 2 who developed opioid problems had histories of drug abuse [31]. This paper was followed by several other publications on opioids for chronic noncancer pain [32; 33; 34; 35]. Each paper cited the prevalence rates of iatrogenic opioid addiction reported by three earlier pain studies [36; 37; 38]:

- Of 11,882 hospitalized patients with a negative substance abuse history who received ≥1 opioid dose, 4 developed addiction.
- A national survey of roughly 10,000 patients treated for burn pain found no cases of addiction.
- Of 2,369 patients treated at a headache center who had access to opioid analgesics, 3 developed problems with their prescribed opioid.

These iatrogenic addiction figures were disseminated through communications to specialists, general practitioners, other providers, administrators, regulators, and the lay public. "Less than 1%" became the message that opioids posed little risk of addiction in patient with pain without substance abuse histories. Substantial support for compassion-based efforts to broaden opioid use for pain control also came from the 1990 opinion paper by the co-author of the landmark paper describing gate control theory that revolutionized the concept of pain [39]. In 1988, the Federation of State Medical Boards (FSMB) released a policy explicitly reassuring physicians they would not face regulatory action for prescribing even large amounts of opioids, assuming it was medically warranted [30]. Physician awareness of the new FSMB policy was promoted by widely circulated publications. For example, the Joint Commission published a guide, supported by Purdue Pharma, stating, "Some clinicians have inaccurate and exaggerated concerns about addiction, tolerance, and risk of death," and "This attitude prevails despite the fact there is no evidence that addiction is a significant issue when persons are given opioids for pain control" [30].

During the 1990s, the American Pain Foundation endorsed more aggressive treatment of chronic pain, while the American Pain Society (APS) promoted the position that pain should be considered a fifth vital sign. The APS and the American Academy of Pain Medicine (AAPM) published a landmark consensus statement in 1997 that stated long-term opioid analgesic use for chronic noncancer pain posed minimal risk of overdose or addiction [30; 40]. The pharmaceutical industry was also instrumental in the movement toward loosening opioid prescribing constraints and broadening the indications for opioid use in managing chronic pain [30; 41]. Professional pain societies wrote consensus statements claiming little risk of addiction or overdose in patients with pain and that long-term opioids were easy to discontinue. In 1997, Congress passed SB402, also known as The Pain Patient's Bill of Rights [42]. In 2001, the Joint Commission issued new standards requiring hospitals to make pain assessment routine and pain treatment a priority. The now familiar pain scale was introduced, with patients asked to rate their pain from 1 to 10 and circle a smiling or frowning face, and pain became the fifth vital sign [43]. Immediately following the release of the new standards, concern was raised that the standards would lead to the inappropriate use of opioids. By 2002, pain as a "fifth vital sign" in the standards was changed to "pain used to be considered the fifth vital sign," and by 2004, this phrase no longer appeared in the Joint Commission's Accreditation Standards manual [44]. The standard that pain be assessed in all patients also remained controversial for two reasons: It seemed inappropriate for some patients due to the nature of their medical condition; and no similar standard existed requiring the universal assessment of other symptoms [44]. Thus, in early 2016, the Joint Commission began revising its pain assessment and management standards, with a focus on acute pain in the hospital setting. Draft standards were published in 2017, implemented in 2018, and revised in 2019 [45; 46].

RETAIL PURCHASES[a] OF PRESCRIPTION OPIOIDS (GRAMS OF DRUG)—UNITED STATES, 2019–2021			
Opioid	**2019**	**2021**	**Change**
Methadone	15,080,444 g	13,866,600 g	-8.01%
Oxycodone	35,929,260 g	31,190,066 g	-13.2%
Fentanyl base	193,531 g	154,574 g	-20.1%
Hydromorphone	987,221 g	1,013,929 g	+2.71%
Hydrocodone	20,040,962 g	17,399,719 g	-13.2%
Morphine	11,966,623 g	9,728,577 g	-18.7%
Codeine	12,105,985 g	9,942,219 g	-17.9%
Meperidine	292,694 g	153,171 g	-47.7%
Total	96,596,720 g	83,448,855 g	-13.6%
[a]Purchasers include pharmacies, hospitals, practitioners, teaching institutions, and treatment programs.			
Source: [50]			*Table 5*

The financial support supplied to professional societies by drug companies helped influence members to change prescribing practices. Patient advocacy groups, often guided by physicians who felt constrained by the prohibition of opioid prescribing and pain specialist organization consensus that chronic pain had been previously undertreated, worked to elevate awareness that pain was untreated and unrecognized [28; 40]. During this time, opioid prescribing for chronic noncancer pain dramatically increased across the country. The movement for more aggressive pain treatment culminated in 2000, when Congress proclaimed 2000–2010 as the Decade of Pain Control and Research [47]. Shifting demographics also contributed to the changing attitudes toward opioid prescribing. With painful chronic illness rates increasing with the overall population age, there came growing awareness of the importance in providing effective pain relief [43].

Pharmaceutical companies began introducing new opioid formulations, and existing opioid products became more widely prescribed (***Table 5***). The theme of minimal abuse liability was widely used in the marketing materials distributed to prescribers and pharmacists [48]. When the escalating rates of addiction, diversion, and fatal overdose involving prescribed opioids became apparent, the same pain specialists and organizations, pain advocacy groups, drug companies, and media reinforced the perception of opioid legitimacy by primarily attributing the growing individual and public health hazard to improper Internet availability, illicit diversion, and the prevalence of societal drug addiction tendencies [49].

THE OXYCONTIN STORY: A CASE STUDY

The story of extended-release oxycodone, marketed as OxyContin, is informative and unique. Although the United States has experienced several waves of widespread prescription drug abuse over the past 150 years, the rapid ascent of OxyContin from market entry to miracle drug for chronic pain to a demonized substance of abuse and diversion on a vast scale is without precedent. Multiple factors facilitated this phenomenon. OxyContin contains a larger amount of high-potency opioid than short-acting opioid formulations. The delayed-release mechanism was easy to circumvent by chewing and swallowing or by crushing the pill and then injecting or snorting the powder. This produced a rapid, powerful opioid effect on par with heroin. Large profits were also possible from illicit sales of OxyContin, which generally commanded a black-market value of $1 per milligram (with higher prices in more rural areas) [51]. In addition, the original product labeling warned against crushing the tablets because rapid release of a potentially toxic amount of oxycodone would ensue, alerting abusers on how to best achieve maximum drug effect. The original labeling also included the FDA-condoned statement that the extended-release (ER) mechanism of OxyContin presented a lower abuse potential than other oxycodone products. Perhaps most importantly, its release coincided with the growing acceptance of opioids in pain treatment and the aggressive sale and marketing tactics of its producer, Purdue Pharma [43].

The timing of product launch was fortuitous. Until the 1990s, Schedule II opioids were primarily limited to use in operating rooms and inpatient settings because they required intravenous or intramuscular administration. This posed a serious obstacle to patients with chronic pain who required high-potency opioids. In response to the increasingly permissive climate and by genuine unmet patient need, several high-dose ER formulations of pre-existing opioids were introduced to market. MS Contin, an ER version of morphine sulfate, was introduced in 1985 but was primarily limited to use in cancer pain, partially a result of the stigma surrounding morphine. OxyContin was introduced in late 1995, at the point in time when prescriber attitudes were shifting from fearing iatrogenic addiction to developing a sense of security with prescribing opioid analgesics [43].

To help ensure product success, innovative approaches were employed to elevate visibility and encourage OxyContin prescribing, as well as highly aggressive marketing and sales tactics.

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OXYCONTIN SALES AND PRESCRIBING, 1996–2002				
Year	**Sales**	**Increase from Previous Year**	**Number of Prescriptions**	**Increase from Previous Year**
1996	$44,790,000	N/A	316,786	N/A
1997	$125,464,000	180%	924,375	192%
1998	$286,486,000	128%	1,910,944	107%
1999	$555,239,000	94%	3,504,827	83%
2000	$981,643,000	77%	5,932,981	69%
2001	$1,354,717,000	13%	7,183,327	21%
2002	$1,536,816,000	13%	7,234,204	7%

Source: [43] *Table 6*

The amount of money spent in promotion, marketing, and sales was unprecedented for an opioid, exceeding $200 million in 2001 alone [52]. Marketing and promotion efforts and the timing of the product launch resulted in a tenfold increase in OxyContin prescribing and sales revenue in just three years' time (***Table 6***).

In addition to the usual doctor-directed ads in medical journals, a novel indirect marketing campaign involving "non-branded education" was implemented. Direct-to-consumer advertising of opioid drugs was prohibited, so the concept of pain relief from opioids was promoted to consumers without explicit mention of OxyContin. The public-education program Partners Against Pain (PAP) was launched, with videos, patient pain journals, and an elaborate website that marketed (to prescribers and patients) the message that pain was widespread and treatable with opioid analgesics [43; 53]. The FDA later stated that the PAP website did provide information about OxyContin specifically and also contained a "Find a Doctor" feature to link consumers to physicians in their geographic area known to be willing to prescribe OxyContin [43].

More than 40 national pain-management and speaker-training conferences were conducted between 1996 and 2001. Thousands of prescribers attended the all-expenses-paid symposia held in resort locations [52]. From 1996 to July 2002, more than 20,000 pain-related educational programs and continuing medical education offerings for prescribers were funded by pharmaceutical sponsorship or financial contribution. This included a program that educated hospital physicians and staff on hospital and postoperative pain treatment compliance with Joint Commission pain standards. Pharmaceutical funding was used to underwrite the cost of the Joint Commission pain management educational programs, including the distribution of educational videos and a book on pain management (sold on the Joint Commission's website) [52]. Pharmaceutical funding has also paid for websites that provided free continuing medical educational on pain management; numerous pain management websites; groups such as the American Chronic Pain Association, the AAPM, and the APS; and a youth-focused website [43].

In 1999, pharmaceutical sales representatives were reportedly given 14,000 copies of a promotional video for physician distribution. Physicians were instructed to encourage patient viewing in their waiting rooms or as a "check-out" item and to use the video as an educational tool for office or hospital staff. The FDA later stated they were not provided the video before distribution for detection of inaccurate or unfounded claims, of which they later found several examples [43]. A patient starter coupon program was initiated that provided patients with a free limited-time prescription. Roughly 34,000 coupons had been redeemed when the program ended in 2001 [43; 52].

Between 1996 and 2000, the internal sales force of the pharmaceutical firm that produces OxyContin grew from 318 representatives to 671, and a bonus system was implemented to encourage OxyContin sales [52]. The company is said to have maintained an active database containing nationwide profiles of individual physicians and their prescribing patterns, allowing for the identification of high-end and low-end OxyContin prescribers by zip code, county, and state; practices with large numbers of patients with chronic pain; and high prescribers of the company's older product MS Contin [52]. Sales representatives were reportedly directed to high opioid prescribers in their sales territories, with the goal of expanding the primary care OxyContin prescribing base. Sales representatives were also directed to call on oncology nurses, consultant pharmacists, hospices, hospitals, and nursing homes [43].

In 1996, the majority of ER opioid prescriptions went to cancer patients, but by 2000, only 3% of OxyContin prescriptions came from oncologists [54; 55]. Opioid medications, and OxyContin in particular, had been successfully promoted as the first-line therapy for an increasingly wide range of moderate-to-severe pain conditions. Family practice physicians became the largest group of OxyContin prescribers, accounting for 21% of prescriptions in 2000 and close to 50% in 2003 [52; 53]. This was followed by the growing concern that, in a managed care system, time constraints imposed on primary care physicians did not allow sufficient time to evaluate and follow patients with complex chronic pain [52].

The most critical issue and source of greatest prescriber concern was the risk of iatrogenic addiction. To help counter this perception, promotion and marketing to healthcare professionals and patients alike emphasized that OxyContin prescribing carried little risk of addiction. Misrepresenting this risk proved costly. In 2007, the pharmaceutical company paid $634 million in fines following guilty pleas from three of its executives to criminal charges for promoting false claims that OxyContin was less addictive and less subject to abuse and diversion than other opioids [52].

The escalating rates of OxyContin misuse were integral to the growing nationwide problem of prescription opioid abuse, diversion, addiction, and overdose. By 2004, OxyContin had become the most prevalent prescription opioid abused in the United States. Predictably, this public health epidemic created a backlash from regulatory and law enforcement agencies [56].

THE PAIN MANAGEMENT MOVEMENT

By the mid-2000s, professional and law enforcement efforts had emerged to curtail OxyContin abuse, including the pain management movement and creation of the pain management subspecialty. However, these efforts had some unintended negative consequences. Pharmacists were tasked with evaluating legal prescription appropriateness through a "drug use review." Encouraged by drug enforcement authorities, some became adversaries of physicians and patients by reporting any out-of-the-ordinary prescribing to the police [56].

Legitimate OxyContin use was also tarnished by negative media coverage suggesting that drug diversion was the result of irresponsible prescribing practices. A 2011 study of OxyContin coverage content in lay media and professional publications found that abuse, addiction, crime, and death were emphasized, typically from law enforcement and the criminal justice system perspectives. The majority of patients with legitimate medical need who benefited from the drug were rarely mentioned. An unfortunate outcome is the stigma sometimes experienced by patients who require OxyContin for long-term pain control [57].

EPIDEMIOLOGY OF CHRONIC PAIN AND OPIOID USE

Chronic pain costs the nation up to $635 billion each year in medical treatment and lost productivity. It also affects about 100 million American adults—more than the total affected by heart disease, cancer, and diabetes combined [7]. The lifetime prevalence of chronic pain ranges from 54% to 80%, and among adults 21 years of age and older, 14% report pain lasting 3 to 12 months and 42% report pain persisting longer than 1 year [7]. An estimated 41% of patients with chronic pain report their pain is uncontrolled, and 10% of all adults with pain suffer from severe, disabling chronic pain.

The increasing prevalence of chronic pain is the result of multiple factors, including the aging population; rising rates of obesity and obesity-related pain conditions, such as joint deterioration; advances in lifesaving trauma interventions; poorly managed post-surgical pain; and greater public awareness of pain as a condition warranting medical attention [7]. In addition, many armed forces veterans have been returning from military action in Afghanistan and Iraq with traumatic injuries and chronic pain, and veterans' care clinicians have been reporting the perception that long-term pain management is lacking support in the veteran healthcare infrastructure [58].

The extent of opioid analgesic use in the United States today is unprecedented in the country's history and unparalleled anywhere in the world. Before 1990, prescribers in the United States were skeptical of prescribing opioids for chronic noncancer pain. But as of 2017, nearly 58 opioid prescriptions were written for every 100 Americans, and more than 17% of Americans had at least one opioid prescription filled, with an average of 3.4 opioid prescriptions dispensed per patient [59]. Sales of opioid analgesics was an estimated $22.66 billion in 2021. Market size is expected to expand at an annual rate of 1.2% between 2022 and 2030 [60].

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 2021 consumption of 26.6 tons (24,131 kg); the majority (26.3 tons) of this were consumed in the United States. Similarly, 3 tons (2,722 kg) of oxycodone were consumed globally in 1990, versus 62 tons (56,246 kg) in 2021, of which 42.3 tons (38,374 kg or 68.2%) were consumed in the United States [61]. With only 4.9% of the world's population, the United States annually consumes more than 85% of all opioid supplies, including [61]:

- 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 nonmedical opioid analgesic users 12 to 17 years of age increased 542% [47]. To assist in monitoring the public health problem associated with prescribed opioids, numerous governmental, nonprofit, 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 (***Table 7***) [62].

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AGENCIES INVOLVED IN COLLECTING AND REPORTING DATA ON NONMEDICAL OPIOID ANALGESIC USE	
Agency [Sponsor]	**Activities**
National Institute on Drug Abuse [NIH, DHHS]	Conducts research involving drug abuse and addiction, tracks trends, disseminates results to improve drug abuse and addiction prevention, treatment, and policy
Monitoring the Future Survey [NIDA, ISR]	Collects data related to drug, alcohol, and cigarette use and attitudes in public and private secondary school students in 8th, 10th, and 12th grade
Drug Abuse Warning Network [SAMHSA]	Monitors drug-related hospital emergency visits and deaths to track the impact of drug use, misuse, and abuse; conducts retrospective review of medical records and case files
Drug Evaluation Network System [TRI, ONDCP]	Generates reports to assist in treatment planning, tracks changes in patient function over time, tracks trends in drug usage, monitors program performance and prepares mandated reports to government and elected officials, maintains an electronic data collection system
The National Epidemiologic Survey on Alcohol and Related Conditions [DHHS/NIH/NIAAA]	Provides information on alcohol use and nonmedical use of prescription opioids (excluding methadone and heroin), sedatives, tranquilizers, and amphetamines in non-institutionalized populations 18 years of age and older
The National Survey on Drug Use and Health [SAMHSA's OAS, DHHS, RTI]	Obtains statistical information related to illicit drug use, administers population-level questionnaires to non-institutionalized residents 12 years of age and older through in-person interviews to obtain data on illicit and prescription drug use
The National Center on Addiction and Substance Abuse at Columbia University [private funding]	Studies and combats substance abuse, surveys children, teens, college students, parents, other adults, prisoners, and women receiving temporary assistance
Researched Abuse, Diversion, and Addiction-Related System [Purdue Pharma, Rocky Mountain Poison Control Center]	Collects product- and locality-specific data; measures rates of abuse, misuse, and diversion to help understand trends; helps develop interventions; assists pharmaceutical companies in regulatory adherence; operates a prescription drug abuse, misuse, and diversion surveillance system
The Arrestee Drug Abuse Monitoring Program [NIJ]	Collects data related to newly booked arrestees regarding drug use, drug and alcohol dependence, treatment, and drug market participation
The National Poison Data System [AAPCC]	Provides a real-time comprehensive poisoning surveillance and toxicovigilance database, operates a uniform data set from the AAPCC
Office of the Medical Investigator (OMI) [city, county, and state governments]	Investigates deaths that come under the jurisdiction of the OMI, including poisoning and drug-related fatalities
AAPCC = American Association of Poison Control Centers, DHHS = U.S. Department of Health and Human Services, ISR = Institute for Social Research, NIAAA = National Institute on Alcohol Abuse and Alcoholism, NIDA = National Institute on Drug Abuse, NIH = National Institutes of Health, NIJ = National Institute on Justice, ONDCP = White House Office of National Drug Control Policy, SAMHSA's OAS = Substance Abuse and Mental Health Services Administration, TRI = Treatment Research Institute.	
Source: [62]	*Table 7*

As of April 2020, 40 states have passed laws that address opioid analgesic prescribing. State-specific legislation, medical and pharmacy boards, Medicaid programs, department of workforce services, and workers' compensation programs have adopted policies, guidelines, and regulations that place limits on prescribing opioid analgesic medications and/or require monitoring of opioid prescriptions. Many insurance companies and managed healthcare organizations have also implemented policies related to limitations on opioid analgesic prescriptions. This has led to a general downward trend in total daily doses of opioids used, use of ER/LA opioid analgesics, and use of high-dose opioids. This trend began even before the release of the 2016 CDC guidelines for opioid prescribing. The use of ER/LA opioid analgesics for chronic pain continues to decline year-over-year. As of 2023, more than 90% of opioid prescriptions have been for immediate-release opioids or short-acting opioids [63].

In 2020, the Drug Enforcement Agency's Automation of Reports and Consolidated Orders System (ARCOS) reported that the number of dosage units distributed nationwide at the retail level (i.e., hospitals, pharmacies, practitioners, treatment programs, and teaching institutions) was down from 2018. However, opioids continued to rank as fifth out of the seventh most distributed controlled prescription drugs. Hydrocodone and oxycodone products were dispensed at more than twice the

rate of any other controlled prescription drug, which remains a steady trend [64]. Although the amount of prescription opioids available on the legitimate market has declined each year since peaking in 2011, the number of prescription opioids available in 2020 remained significant. ARCOS indicated that 9.7 billion dosage units of opioid controlled prescription drugs were manufactured and distributed in 2019. Of that number, approximately 78% were oxycodone and hydrocodone products [64].

Prescribing rates are down overall, but they vary widely between states, particularly at the county level. The nationwide prescribing rate for 2018 was 51.4 prescriptions per 100 persons, yet some counties had rates that were seven times higher than the national average. For example, Alabama and Arkansas had the highest prescription rates (just under 100 prescriptions for 100 people), while New York and Hawaii had the lowest rates at 34.0 and 33.4 prescriptions per 100 people, respectively [64].

FACTORS THAT INFLUENCE OPIOID ANALGESIC PRESCRIBING

A decision to prescribe opioids is based on clinician knowledge and judgment and also on patient preference, availability of non-opioid pain treatment approaches, the complexities and bias in third-party reimbursement, aggressive pharmaceutical marketing, and medico-legal concerns. These and other factors have tended to skew the standard of care toward reliance on opioids for long-term chronic pain management in the past few decades [8].

The use of patient satisfaction as a barometer of clinician skill may also influence opioid analgesic prescribing. Satisfaction with clinical care can be obtained from patient surveys, commonly including questions about how adequately their pain was addressed by the provider. Numerous for-profit provider-grading websites offer patients a forum to broadcast their opinions of care received from physicians. Healthcare professionals are likely to get a poor rating from patients who were refused opioids over abuse concerns, and reimbursement and job security can be adversely impacted by negative patient survey ratings in some institutions [65].

The financial structure of many managed care firms and third-party carriers incentivizes pain treatment and discourages substance abuse or addiction treatment. From a financial reimbursement perspective, the time spent providing patient education and counseling related to addiction issues has become one of health care's least valued commodities. This is especially the case in emergency department (ED) settings, where evaluation is often based on patient volume and not on time spent with individual patients. As such, it is faster and pays better to diagnose pain and prescribe an opioid than to diagnose and treat addiction [65].

Increasing Population Rates of Chronic Pain

Any discussion of the rising rates of opioid analgesic prescribing should also acknowledge the increasing prevalence of chronic pain in the United States, with data showing increasing rates over the past several decades that are projected to continue in the future. Musculoskeletal conditions are the most common type of chronic pain, with back pain the most common type of chronic musculoskeletal pain [66]. Increases in low back pain prevalence and associated disability have been quantified in several studies. For example, an investigation of low back pain rates over a 40-year period found increases in prevalence from 8.1% in 1956–1958 to 17.8% in 1994–1995 in men, and 9.1% to 18.2% in women [67]. A comparison of back pain prevalence in North Carolina between 1992 and 2006 found an increase in chronic, impairing low back pain, from 3.9% in 1992 to 10.2% in 2006, and an 11.6% annual increase in healthcare utilization and disability [68]. Data from the National Center for Health Statistics estimate that in 2021 20.9% (51.6 million) of adults in the United States had chronic pain and 6.9% (17.1 million) had high-impact chronic pain (defined as pain that limits life or work activities on most days or every day in the past six months), with higher prevalences of both types of pain reported among women, older adults, previously but not currently employed adults, adults living in poverty, adults with public health insurance, and rural residents [69].

OPIOID ANALGESIC-RELATED MORBIDITY

There are a number of ways that the larger picture of opioid analgesic-related morbidity may be examined. Because the effects of opioid analgesic misuse can manifest in many ways in a variety of settings, it is important to examine data from different sources in order to get an accurate picture of opioid-related morbidity in the United States.

Emergency Department Admissions

The legacy Drug Abuse Warning Network (DAWN) was established in 1972 by the Drug Enforcement Administration to track and publish data collected from participating states on ED visits resulting from substance misuse or abuse, adverse reactions, drug-related suicide attempts, and substance abuse treatment [70]. By its final year in 2011, legacy DAWN had collected data from metropolitan areas in 37 states, with complete coverage in 13 states. Although their total figures did not capture all 50 states, the population rates were representative and able to be extrapolated to the United States as a whole [71].

In 2011, the overall admission rate for misuse or abuse of opioid analgesics (excluding adverse reactions) was 134.8 per 100,000, an increase of 153% compared with 2004. In the 13 states involved in the legacy DAWN network, the top four opioid analgesics involved in drug-related ED visits for 2011 were various formulations of oxycodone (175,229), hydrocodone (97,183), methadone (75,693), and morphine (38,416). Between 2004 and 2011, ED admissions increased 74% for methadone, 220% for oxycodone, 96% for hydrocodone, and 144% for morphine. Importantly, there was no meaningful change in ED admission rates involving opioid analgesics between 2009 and 2011. If this is also borne out by subsequent data, it strongly suggests a plateau in the misuse and abuse rates of these agents [71].

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As of 2020, the Substance Abuse and Mental Health Services Administration (SAMHSA) re-established DAWN and will retain the important aspects of legacy DAWN. In comparison to legacy DAWN, the re-established DAWN functions as a smaller-scale sentinel surveillance system, or an early-warning system. The new DAWN will focus on detecting "outbreaks" (i.e., sudden increases in ED visits for specific drugs), identifying new and novel psychoactive substances, monitoring the magnitude of the health effects from substance use (as reflected in ED visits), and documenting the geographic, temporal, and demographic distribution of the problems to inform planning and policy at the local, state, and national levels [72].

Nonmedical Use of Prescription Opioids

In 2021, 9.2 million people reported nonmedical use of opioid analgesics (i.e., use without a prescription or for the non-analgesic effect) and 1.4 million were first-time nonmedical users that year [73]. An estimated 2.6 million people misused oxycodone products (including OxyContin) in the past year (1.2% of the population) [73]. The most frequent initial (past year) drug used was cannabis (52.5 million), followed by nonmedical use of prescription opioids (9.2 million), hallucinogens (7.4 million), nonmedical use of tranquilizers (4.9 million), stimulants (4.9 million), cocaine (4.8 million), methamphetamine (2.5 million), inhalants (2.2 million), and heroin (1.1 million) [73].

Among people 12 years of age or older in 2021, 3.3% (9.2 million) reported opioid misuse in the past year. The percentage was lowest among adolescents 12 to 17 years of age (1.9% or 497,000 people). Percentages were similar among young adults 18 to 25 years of age (3.1% or 1.0 million people) and adults 26 years of age or older (3.5% or 7.7 million people) [73].

Rates of Prescription Opioid Abuse and Addiction

The vast majority of people who misused opioids in the past year misused prescription pain relievers. Specifically, 8.7 million people 12 years of age or older misused prescription pain relievers in the past year, compared with 1.1 million people who used heroin [73]. In 2021, the majority (8.1 million) of the 8.7 million misusers of prescription pain relievers misused only prescription pain relievers in the past year—they had not used heroin. An estimated 574,000 people misused prescription pain relievers and used heroin in the past year, and 525,000 people used heroin in the past year but had not misused prescription pain relievers [73].

Widespread opioid analgesic prescribing and nonmedical use, abuse, and dependence are not unique to the United States. Canadian estimates for 2009 indicated that of the total population, 19.2% used prescription opioid analgesics, including nonmedical use by 4.8%, and that 0.4% used the drugs nonmedically to get high. The past-year nonmedical use prevalence of 1 in 20 adults was comparable to U.S. rates. Although the study found high rates of prescribed opioid analgesic use and nonmedical use, most noteworthy was the conclusion that opioid analgesic prescribed use, nonmedical use, and nonmedical use to get high was not associated with the level of prescription opioid dispensing. This finding stands in contrast to the stream of reports over the past decade from the CDC, the DEA, and other governmental agencies in the United States [74].

SAMHSA data do differentiate the underlying basis of misuse. For instance, a person who took or received a prescription opioid from a relative or friend for a headache is recorded as a nonmedical user (abuser); although placed in the same category as someone who stole prescription opioids from a medicine cabinet to get high, the motivations and possible interventions for the respective problems are entirely different. The importance of this distinction is clear in a large 2008 survey of high school seniors, which found that 12.3% had used opioid analgesics for nonmedical reasons at some point [75]. This is similar to a 2012 study of 7,374 high school seniors, which found that 12.9% reported lifetime nonmedical use of prescription opioids [76]. A multi-cohort national study of more than 8,000 high school seniors found that 36.9% of past-year nonmedical users of prescription opioids obtained the medications from their own previous prescriptions. Analyses indicated that these users were primarily motivated by a desire to relieve physical pain [77]. This should lead to exploration of important public health questions, such as why so many young people suffering from untreated (or mistreated) physical pain resort to self-medication [76; 77].

Opioid Use Disorders in Patients with Pain Receiving Long-Term Opioid Analgesics

The literature examining opioid use disorder incidence in patients with chronic pain receiving opioid analgesic therapy have reported rates of addiction developing during opioid therapy ranging from 0.03% to 50% [78; 79]. These vast differences are mainly the result of widely varying criteria to define opioid addiction. Many of the studies used diagnostic criteria according to the DSM-IV, or the DSM-III in studies that began before 1994. The DSM-III and IV criteria include tolerance and withdrawal as diagnostic criteria, which can reflect physical dependence that is an expected development of long-term opioid therapy. Other DSM diagnostic criteria may also describe common non-addiction based experiences of patients with pain who are receiving long-term opioid therapy, such as using the medication in higher amounts or for a longer term than intended and a persistent desire or unsuccessful attempts to cut down, control, or halt the use of the opioids [80]. Also, DSM criteria require the patient experience of impaired function or distress resulting from their opioid use. Many of those with chronic pain report clinically significant dysfunction and distress from their chronic pain; some studies do not clarify whether pain or the opioid is causing the reported dysfunction and distress. For these reasons, more recent pain researchers have concluded that DSM criteria are not applicable and may be misleading as a diagnostic basis in patients with chronic pain [78; 81].

One study that controlled for the improper fit of DSM opioid addiction criteria in patients receiving long-term opioid therapy followed a group of patients with sickle cell anemia [82]. Researchers found that 31% of patients receiving opioids developed opioid dependence according to the DSM-IV criteria. When pain-related symptoms that actually accounted for positive diagnostic criteria were removed, the addiction incidence fell to 2% [82]. In a review of 24 studies enrolling 2,507 patients with chronic pain with a 26.2-month average duration of opioid therapy, the overall opioid addiction rate was 3.27% [79]. A 2013 study evaluated the rate of drug misuse and illicit use in 1,350 patients with a pain duration greater than one year who were currently prescribed opioids for three months or longer and enrolled in an interventional pain program. The study found that 1.3% were using non-prescribed prescription drugs and 7.9% were using illicit drugs (primarily cannabis; substantially fewer for cocaine and methamphetamine). The authors concluded the rates they found in patients receiving opioids were comparable to those of the general population [83].

Treatment Admissions for Opioid Use Disorders

Among persons 12 years of age or older with a past-year opioid use disorder due to their use of heroin or misuse of prescription pain relievers, 22.1% (533,000 people) received medication-assisted treatment in the past year [73].

Diversion of Prescription Opioids

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. This information carries with it substantial public policy and regulatory implications. The 2021 NSDUH data asked non-medical users of prescription opioids how they obtained their most recently used drugs [73]. 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 2018), 7.3% bought them from a friend or relative, and 7.9% bought them from a drug dealer or other stranger. Less frequent sources included stealing from a friend or relative (3.7%); multiple doctors (3.2%); theft from a doctor's office, clinic, hospital, or pharmacy (0.7%) (vs. 0.7% in 2018); and some other way (4.0%) [73].

Neonatal Abstinence Syndrome (NAS)

Rates of opioid misuse may also be tracked by unintended effects of use during pregnancy on newborns. Cases of neonatal abstinence syndrome (NAS)—a group of problems that can occur in newborns exposed to prescription opioids or other drugs while in the womb—grew by 83% in the United States between 2010 and 2017 [84].

OPIOID ANALGESIC-RELATED MORTALITY

Opioid analgesics may result in deaths due to unintentional or intentional overdose or intoxication-related accidents. However, the majority of data focus on unintentional overdose. The rates of fatal toxicity involving prescription opioid analgesics have escalated in tandem with the increasing rates in opioid analgesic prescribing, abuse, addiction, and diversion. Unfortunately, additional valuable information is not revealed by the mortality data, such as whether the potential cause of the fatality was opioid ingestion for intoxication or for pain control, or whether the decedent was taking the medication as prescribed, using the opioid nonmedically (e.g., for insomnia control), using the medication plus someone else's prescribed opioid for poorly managed pain, or taking someone else's prescribed opioid to get high. Also unknown is the relative contribution of the opioid to the fatality. In one postmortem study of fatalities involving prescription opioids, 79% of decedents also tested positive for alcohol and other drugs [85]. In the absence of more details surrounding opioid fatalities, crafting preventive measures is difficult, and estimates of the true fatality rate from prescription opioids remain elusive.

Regional differences have been found in fatal drug overdose involving opioids, with the highest rates occurring in the Southwest and Appalachian regions. Differences between states have also been found. Data from 2021 indicate the highest fatal drug overdose rates occurred in West Virginia (90.9 per 100,000), Tennessee (56.6 per 100,000), Louisiana (55.9 per 100,000), Kentucky (55.6 per 100,000), New Mexico (51.6 per 100,000), and Ohio (48.1 per 100,000. In 2020, 91,799 drug overdose deaths occurred in the United States. The age-adjusted rate of overdose deaths increased by 31% from 2019 (21.6 per 100,000) to 2020 (28.3 per 100,000). Opioids were involved in 68,630 overdose deaths in 2020 (74.8% of all drug overdose deaths) [86]. Significant increases in drug overdose death rates during this period were primarily seen in California, Mississippi, Virginia, and South Carolina [87].

According to one analysis, nearly one in four people on Medicaid received prescription opioids in 2015 [88]. The report analyzed 1.8 million opioid prescriptions written for 3.1 million Medicaid members across 14 states. According to the CDC, Medicaid patients are prescribed opioids at twice the rate of non-Medicaid patients and are at six times the risk of overdose [89]. However, essential information was omitted in this CDC report but uncovered by an investigation into Washington state opioid fatalities [90]. Left out of the CDC publication was the policy decision in early 2004 by the State of Washington to list methadone as a preferred opioid analgesic, as a cost-cutting measure. Morphine was the only other long-acting opioid placed on the preferred analgesics list. Methadone fatalities increased from 140 in 2002 to 256 in 2004. Many of these fatalities involved the combination of methadone and other prescribed medication, particularly benzodiazepines and antidepressants; of the 274 methadone-related fatalities in 2009, prescribed medications for anxiety or other mental-health concerns were found in 43% of decedents. The number of methadone fatalities in 2006 was 300% greater than the number attributed to any other long-acting pain reliever. Although the escalation in methadone fatalities had become obvious, the cost-cutting objectives were significant and state officials maintained the stance that methadone was safe and effective [91].

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EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society of Interventional Pain Physicians recommends methadone for use after failure of other opioid therapy and only by clinicians with specific training in its risks and uses.

(https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed August 15, 2023.)

Level of Evidence: I (Evidence obtained from multiple relevant high quality randomized controlled trials for effectiveness)

Gender Differences

The opioid overdose rate among women has increased faster than it has in men. From 1999 to 2010, overdose fatality increased by more than 400% in women, compared to 265% for men; during this period, nearly 48,000 women died of opioid analgesic overdose. In aggregate, women tend to possess background characteristics and opioid analgesic use patterns that may contribute to overdose vulnerability. Women are more likely to experience chronic pain, receive prescriptions for opioid analgesics, receive higher doses of opioids, and use opioids for longer periods than men. Substance use disorders involving opioid analgesics are thought to develop more rapidly in women, and women may be more likely to obtain opioid prescriptions from multiple prescribers than men [92].

Women 25 to 54 years of age have the highest rate of ED admission for opioid misuse or abuse, and the greatest risk of prescription opioid fatality occurs in women 45 to 54 years of age. Non-Hispanic white and American Indian or Alaska Native women have the highest mortality risk from prescription opioids, and opioid analgesics are involved in 1 in 10 suicides among women [92].

Overdose Fatality and Prescribed Opioid Dosage

Several studies have reported a positive association between high-dose opioid prescribing and overdose risk. However, these studies utilized methods in design and data analysis that cast doubt on the results, such as failure to control for the possible effect of opioid abuse on overdose outcomes and differences in the indications, formulations, and opioid products in patients prescribed high versus low dosing [93].

A study was conducted to re-examine the relationship between opioid dose and overdose risk while controlling or eliminating the methodological shortcomings in previous studies. The records of 38,861 patients prescribed morphine ER, transdermal (patch) fentanyl, or buprenorphine patch between 2005 and 2010 were evaluated. High-dose was defined as 120 mg morphine equivalent dose (MED) or more; low-dose included 30 mg MED or less. The rates of overdose were 0.7% with morphine ER, 0.4% with fentanyl patch, and 0.3% with buprenorphine patch. The relative risk of overdose among patients prescribed high doses was 1.44 for morphine ER, 1.51 for fentanyl patch, 0.78 for buprenorphine patch, and 1.18 when all three opioids were combined. These results indicate a roughly 1.5 times greater overdose risk with high-dose morphine and fentanyl than with low-dose, no difference in overdose risk between high- and low-dose buprenorphine, and an overall overdose risk markedly lower than previous reports [93].

This data should be considered tentative as it was presented at a conference and, as of 2023, has not yet been published in a peer-reviewed journal. As with the previous research, this study was performed retrospectively and not prospectively, which can lessen the validity of the results. However, in light of these limitations, the results provide a credible counterbalance to previously published figures.

Contributory and Risk Factors for Overdose

The reasons for opioid analgesic overdose fatalities are multifactorial and include prescriber behaviors, patient contributory factors, nonmedical use patterns, and systemic failures. Risk factors identified for fatal opioid toxicity include [6]:

- Prescriber error due to knowledge deficits
- Patient nonadherence to medication regimen
- Unanticipated medical and mental health comorbidities, including substance use disorders
- Co-administration of other CNS-depressant drugs, including alcohol, benzodiazepines, and antidepressants
- Sleep-disordered breathing (e.g., sleep apnea)
- Body mass index of 30 or greater

Additional factors specifically contributing to methadone fatality include [94]:

- Payer policies that encourage or mandate methadone as first-line therapy
- Methadone prescribing in opioid-naïve patients
- Lack of prescriber knowledge of methadone pharmacology

A population-based study examined patterns and characteristics of opioid users in Ontario, Canada, whose cause of death involved opioid toxicity [95]. Between 2006 and 2008, 2,330 drug-related deaths were identified, of which 58% were partially or entirely attributed to opioids. The manner of death was classified by a coroner as accidental (68%), undetermined (16.3%), or suicide (15.7%). Among decedents, at least 7% ingested opioids that were prescribed to friends or a family member; 19% altered the route of administration through injection, inhalation, or chewing a transdermal patch; 3% had been released from incarceration just before their death; and 5% had switched from one opioid to another near the time of death [95]. Differences were found between decedents who died accidentally versus suicide. A personal history of substance abuse, enrollment in a methadone maintenance program, cirrhosis, hepatitis, and cocaine use were significantly

associated with accidental death. Mental illness, previous suicide attempts, chronic pain, and a history of cancer were significantly associated with death by suicide.

Methadone

Historically, methadone was used primarily as pharmacotherapy for heroin addiction. During the 1990s, however, methadone gained increased acceptance for use as an analgesic, and methadone began to be prescribed to outpatients with moderate-to-severe noncancer pain. Prescribing rates soared over the next decade; comparison of methadone sales quantity between 1997 and 2007 shows an increase of 1293% [96; 97]. This rising use of methadone occurred simultaneously with concerns over the abuse potential of OxyContin and the search for a relatively inexpensive long-acting opioid analgesic alternative [98].

By 2008, two-thirds of methadone prescriptions were for pain treatment. The unique pharmacologic properties of methadone make its use in pain management complex, with greater potential for hazard than other prescribed opioids. Prescribers familiar with using methadone as opioid addiction treatment may be unaware that suppression of opioid withdrawal symptoms lasts 24 or more hours, while the analgesic duration is 4 to 8 hours, despite a half-life exceeding 60 hours in some patients. Accidental overdose fatalities can occur when patients re-administer methadone when the analgesia wears off and pain returns, potentially elevating plasma concentrations to life-threatening levels. These same pharmacological properties also imperil those who use it illicitly. Opioid abusers often co-administer benzodiazepines, which greatly elevates lethality risk with methadone. Concurrent use of alcohol poses the same risk [98].

Since the mid-2000s, methadone has become disproportionately represented in cases of opioid analgesic fatality. Based on data showing that 70% of fatalities among those prescribed methadone occurred in the first seven days of treatment, the FDA changed the methadone labeling in 2006 to lengthen dosing intervals from every 3 to 4 hours to every 8 to 12 hours; the initial recommended dose of 2.5–10 mg was unchanged [6; 99]. In 2008, use of the highest oral dose preparations, 40 mg, was prohibited from use in pain treatment and restricted to addiction therapy [94].

Mortality Risk in Highly Controlled Inpatient Settings

In addition to the well-publicized risk of overdose fatality with prescribed and diverted opioid analgesics, it is worth mentioning that use of opioid analgesics carries risk even under the most tightly controlled conditions. In 2012, the Joint Commission released a *Sentinel Event Alert* entitled "Safe Use of Opioids in Hospitals," which referenced database reports of death or serious morbidity between 2004 and 2011. Of all events resulting in serious morbidity or mortality, 47% resulted from wrong medication dose errors, 29% resulted from inadequate patient monitoring, and 11% were due to other factors, including excessive dosing, medication interactions, and adverse drug reactions. Prescriber knowledge deficits in opioid pharmacology and optimum opioid route of administration (e.g., oral, parenteral, transdermal patches) accounted for some of the serious adverse patient outcomes [100]. The Joint Commission findings of serious opioid-related morbidity and mortality even when administered under highly controlled conditions and correlational data that show increased prescription opioid abuse and overdose fatality with increased opioid prescribing suggest that adverse outcomes occur at a fixed ratio to overall use [100].

Chronic Pain and Suicide by Overdose

Prolonged intense pain can destroy quality of life and the will to live, driving some patients to suicide [39]. The growing concern over opioid addiction and fatal overdose have obscured the relevant problem of intentional overdose. For many individuals, committing suicide is a way out of a situation or problem causing extreme suffering. According to DAWN, an estimated 228,366 ED visits for drug-related suicide attempts occurred in 2011 [101]. This was a 51% increase in these types of visits in individuals older than 11 years of age compared with 2005 [102]. There was a 58% increase in individuals 18 to 29 years of age, and a 104% increase in those 45 to 64 years of age [102]. Approximately 39% involved alcohol and 11% involved illicit drugs [101; 102].

Although an accurate estimate of the number of suicide attempts and completions is unknown because intent is often misclassified or not classified, risk factors for suicidal ideation are very high in the chronic pain population. Many patients with pain experience concurrent depression, and some have histories of alcohol and substance abuse. Multiple studies have shown rates of suicidal ideation and suicide attempts as high as 50% in patients suffering from chronic pain [103]. An estimated 50% of patients with chronic pain have had serious thoughts of committing suicide due to their pain disorder, and drug overdose is the most commonly reported plan for committing suicide (75%) in these patients [104; 105]. The Canadian Community Health Survey found that, after adjusting for sociodemographics and acute mental disorders and comorbidities, the presence of one or more chronic pain conditions significantly elevated the risk of suicidal ideation and suicide attempts [106]. A literature review found that risk of suicide completion was doubled in patients with chronic pain relative to non-pain controls [107].

UNTREATED/UNCONTROLLED PAIN AND MORBIDITY/MORTALITY

Mortality Risk

A link between chronic uncontrolled pain and adverse health outcomes has been identified in previous research, and the results of a 2010 study reaffirmed this association and uncovered a significant mortality risk not previously identified. Over a 10-year period, a prospective longitudinal study collected annual mortality information from a cohort of 6,940 primary care patients [108]. Survival among those reporting moderate-to-severe interference from chronic pain was significantly worse than survival among those reporting mild or no chronic pain

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or interference. After adjusting for sociodemographic factors and long-term disabling illness, moderate-to-severe chronic pain inflicted a 68% greater mortality risk than cardiovascular disease [108]. While considerable attention has been given to the risk of fatal toxicity and overdose involving opioid analgesics, these data suggest the mortality risk of uncontrolled, severe, chronic pain surpasses that of accidental death from toxicity or overdose with prescribed opioid analgesics.

Alterations in Brain Structure and Function

Substantial evidence indicates that poorly controlled acute pain can induce neuroplastic changes that underlie the development and perpetuation of chronic pain. Evidence from studies of uncontrolled chronic pain are now documenting changes in brain morphology, such as decreased prefrontal cortex gray matter volume in patients with chronic back pain or fibromyalgia [109]. Diminished prefrontal cortex gray matter volume is associated with adverse functional changes and decreased patient ability to engage in behaviors that can inhibit pain experience [109]. One study compared the brain morphologies of patients with chronic back pain to control subjects, and found 5% to 11% less neocortical gray matter volume among patients with back pain, an association between pain duration and volume reduction, and a loss in gray matter volume equivalent to the effects from aging 10 to 20 years [110].

ARRESTEE DATA

Researchers have found a distinctive pattern in the lifespans of drug abuse epidemics. This pattern reflects the escalating and declining prevalence in the use of a substance, the projected course into the near future, and prevalence rate variation across localities. The phases common to all drug epidemics are incubation, expansion, plateau, and decline in use of the drug. Arrestee data are a valuable source of information for tracking drug use trends and are consistent or slightly ahead of drug use data collected from general population studies in measuring drug epidemic phenomenon. To better understand the problem of prescription opioid abuse, information was obtained from 41,501 adult male arrestees in nine geographic locations. Arrestees provided data on their past three-day opioid analgesic use. Data from 2000–2003 were compared with data from 2007–2010. By location, the prescription opioid epidemic phase and the 2010 rate of past three-day opioid analgesic use by arrestees were [111]:

- Atlanta: 4% (never became an epidemic)
- Charlotte: 8% (plateau, possibly declining)
- Chicago: 3% (never became an epidemic)
- Denver: 7% (never became widespread, now declining)
- Indianapolis: 16% (plateau)
- Manhattan: 6% (plateau)
- Minneapolis: 8% (plateau)
- Portland: 15% (plateau, possibly declining)
- Sacramento: 12% (plateau)

These results illustrate the uneven geographic distribution of the prescription opioid use epidemic. It is also clear that prevalence rates are stabilizing or declining in all localities. These arrestee data indicate the epidemic has likely peaked and predict the decline in first-time and past-year use and an increase in prescription opioid addiction and treatment-seeking rates. In susceptible persons, progression in severity of a substance use disorder to addiction often occurs over many years. Persons who now meet diagnostic criteria for opioid analgesic addiction, and may be seeking help, probably began their use during an earlier phase of the epidemic.

MITIGATING RISK IN OPIOID PRESCRIBING PRACTICE

BACKGROUND

As discussed, pain treatment, especially in the context of opioid prescribing, is defined as inappropriate by its non-treatment, inadequate treatment, overtreatment, or continued use of ineffective treatment [10]. Inappropriate pain treatment with opioid analgesics elevates the risk of uncontrolled pain, possibly serious adverse side effects, and abuse and diversion. Therefore, clinicians who treat patients with chronic pain are required to use strategies that assess and mitigate the risk of abuse liability inherent in opioids. Although risk assessment and mitigation strategies have been developed to decrease the problem of prescribed opioid abuse, diversion, and overdose, their use can also reduce the development of serious side effects and help ensure the treatment selected is benefiting the patient [112].

The 2011 Institute of Medicine report *Relieving Pain in America* reinforced the importance of framing chronic pain as a unique chronic disease state with complex neurophysiological, emotional, and social components, making its management distinct from that of acute pain [7]. Treating chronic pain differs from acute pain by the duration, multimodal approach, and risk mitigation of the therapy. Clinicians may fear that managing the issues surrounding opioid analgesic prescribing render the practice too difficult or complex [112]. To assist in the dual need of protecting one's clinical practice while reducing opioid abuse, the FSMB released a model policy for opioid analgesic prescribing in 2013. This policy was the result of identification of harmful but remediable factors contributing to pain undertreatment and inappropriate opioid prescribing, including [10]:

- Knowledge gaps in medical standards, current evidence-based outcomes, guidelines for appropriate pain treatment, and regulatory policies
- Prescriber concerns that legitimate opioid prescribing will lead to unnecessary scrutiny by regulatory authorities
- Conflicting information in existing clinical guidelines
- Prescriber concerns of patient deception to obtain drugs for abuse and fears of precipitating addiction

CHARACTERISTICS OF APPROPRIATE AND INAPPROPRIATE OPIOID PRESCRIBING	
Medically Legitimate Pain Management and Prescribing	**Inappropriate Pain Management and Prescribing**
Based on sound clinical judgment and current best clinical practices	Inadequate attention in initial assessment to clinical indication or patient risk of opioid problems
Appropriately documented	Inadequate monitoring
Demonstrable patient benefit	Inadequate patient education and informed consent
Occurs during the usual course of professional practice	Unjustified dose escalation without sufficient attention to risks or alternative treatments
A legitimate physician-patient relationship exists	Excessive reliance on opioids, especially high-dose opioids, for chronic pain
Prescribing or administration appropriate to diagnosis	Failure to use risk assessment tools
Careful follow-up monitoring of patient response and safe patient use	
Demonstration of adjustment to therapy, as needed	
Documentation of appropriate referrals, as necessary	
Source: [10]	*Table 8*

Prescribers were held to a standard of safe and best clinical practice, the general points of which include [10]:

- Prescribers should know best clinical practices in opioid prescribing, associated risks of opioids, assessment of pain and function, and pain management approaches. Pharmacologic and nonpharmacologic modalities should be used on the basis of current knowledge in the evidence base or best clinical practices.
- Pain should be assessed and treated promptly, with therapy selection based on the nature of the pain, treatment response, and patient risk level for developing opioid problems.
- Prescribers should use safeguards to minimize misuse and diversion risk of opioid analgesics.
- In allegations of inappropriate pain management, the Board will not take disciplinary action for deviation from "best practices" when medical records show reasonable cause for deviation.

The model policy additionally stated that physicians would not be sanctioned on the sole basis of medically legitimate opioid prescribing (***Table 8***).

In 2015, the FSMB appointed a workgroup to review and analyze the original policy document as well as other state and federal policies on the prescribing of opioids in pain treatment, including advisories issued by the CDC and the FDA [113]. In April 2017, the FSMB adopted the *Guidelines for the Chronic Use of Opioid Analgesics*, an update to the original model policy that includes recommendations identified by the workgroup. The stated goal of this document is to provide state medical and osteopathic boards with an updated guideline for assessing physician management of pain, so as to determine whether opioid analgesics are used in a manner that is both medically appropriate and in compliance with applicable state and federal laws and regulations [113].

The FSMB 2017 Guidelines communicate the message that pain management is an important area of patient care, integral to medical practice; and that opioid analgesics may be necessary for pain control. In order to implement best practices for responsible opioid prescribing, clinicians should understand the relevant pharmacologic and clinical issues in the use of opioid analgesics and should obtain sufficient targeted continuing education and training on the safe prescribing of opioids and other analgesics as well as training in multimodal treatments. The Guidelines focus on the general overall safe and evidence-based prescribing of opioids and treatment of chronic, non-cancer pain, with the specific limitation and restriction that they do not operate to create any specific standard of care. A variety of strategies may be used to achieve the goals of the Guidelines, including the patient's level of pain, preferences of the clinician and the patient, available resources, and other concurrent issues. The Guidelines do not encourage the prescribing of opioids over other pharmacological and nonpharmacological means of treatment. Pain management should be viewed as essential to both the quality of medical practice and to the quality of life for patients who suffer from pain. The Guidelines are not intended for the treatment of acute pain, acute pain management in the perioperative setting, emergency care, cancer-related pain, palliative care, or end-of-life care. They apply most directly to the treatment of chronic pain lasting more than three months in duration or past the time of normal tissue healing [113].

ASSESSING OPIOID BENEFIT AND RISK OF MISUSE

In deciding whether to prescribe an opioid analgesic for chronic pain, clinicians should perform, and document in the record, an assessment of the potential benefits and risks to the patient. The elements of such an assessment include [113]:

- Pain indications for opioid therapy
- Nature and intensity of pain
- Past and current pain treatments and patient response

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- Comorbid conditions
- Pain impact on physical and psychological 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 there is a history of substance abuse, active or in remission, consult an addiction specialist before starting opioids [113]. In active substance abuse, do not prescribe opioids until the patient is engaged in a treatment/recovery program or other arrangement made, such as addiction professional co-management and additional monitoring. When considering an opioid analgesic (particularly ER or LA types), one must always weigh the benefits against the risks of overdose, abuse, addiction, physical dependence and tolerance, adverse drug interactions, and accidental ingestion by children [114].

RISK ASSESSMENT TOOLS

Risk assessment involves a determination of whether potential opioid benefits outweigh the potential risks. The individual and public health consequences of prescription opioid abuse, addiction, diversion, and overdose justify assessment and risk stratification in every patient considered for long-term opioid therapy [115]. Patients with chronic pain and past or current alcohol or drug abuse, psychiatric illness, or serious aberrant drug-related behaviors should still be considered for opioid therapy, but with tighter monitoring conditions and consultation from mental health or addiction specialists. Pain management outcomes are negatively affected by untreated psychiatric comorbidity, and proper assessment can identify and lead to the treatment of these conditions [116]. Periodic reassessment is necessary because patient circumstances and the benefit/risk balance of opioid therapy can change, due to alterations in the primary pain condition, comorbid disease, or psychological or social circumstances [115].

Before Opioid Therapy Initiation

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 tool use to help determine patient risk level, most screening tools have not been extensively evaluated, validated, or compared to each other, and evidence of their reliability is poor [97]. In addition to screening and assessment tools, urine drug testing, monitoring of prescribing practices, prescription monitoring programs, opioid treatment agreements, and utilization of universal precautions are essential. Presently, a combination of strategies is recommended to stratify risk, to identify and understand aberrant drug-related behaviors, and to tailor treatments accordingly [117].

The American Society of Interventional Pain Physicians recommends screening for opioid abuse, as it will potentially identify opioid abusers and reduce opioid abuse. (https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed August 15, 2023.)

Level of Evidence: II (Evidence obtained from at least one relevant, high-quality randomized controlled trial or multiple relevant moderate- or low-quality randomized controlled trials)

Opioid Risk Tool

The Opioid Risk Tool (ORT) is a five-item assessment to help predict aberrant drug-related behavior. It is also used to establish patient risk level through patient categorization into low, medium, or high levels of risk for aberrant drug-related behaviors based on responses to questions of previous alcohol/drug abuse, psychological disorders, and other risk factors [27].

Screener and Opioid Assessment for Patients with Pain—Revised

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 [118].

CAGE and CAGE-AID

The original CAGE (Cut down, Annoyed, Guilty, and Eye-opener) Questionnaire consists of four questions designed to help clinicians determine the likelihood that a patient is misusing or abusing alcohol. These same four questions were adapted to include drugs (CAGE-AID), and this tool may be used to assess the likelihood of current substance abuse [119].

Diagnosis, Intractability, Risk, Efficacy Tool

The Diagnosis, Intractability, Risk, Efficacy (DIRE) tool is a clinician-rated questionnaire used to predict patient compliance with long-term opioid therapy [120]. Patients scoring lower on the DIRE tool are poor candidates for long-term opioid analgesia.

Mental Health Screening Tool

The Mental Health Screening Tool is a five-item screen that asks about a patient's feelings of happiness, calmness, peacefulness, nervousness, and depression in the past month [121]. A lower score on this tool is an indicator that the patient should be referred to a specialist for pain management.

PATIENT RISK STRATIFICATION
Low Risk
Definable physical pathology with objective signs and reliable symptoms
Clinical correlation with diagnostic testing including magnetic resonance imaging, physical examination, and interventional diagnostic techniques
With or without mild psychological comorbidity
With or without minor medical comorbidity
None 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, 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 radiological evaluation, physical examination, or diagnostic interventions
Moderate psychological problems, well-controlled by therapy
Moderate coexisting medical disorders well controlled by medical therapy and which are not affected by chronic opioid therapy such as central sleep apnea
Those who develop mild tolerance but not hyperalgesia without physical dependence or addiction
Past 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 their normal daily lives
High Risk
Widespread pain without objective signs and symptoms
Pain involving more than three regions of the body
Aberrant drug-related behavior
History of misuse, abuse, addiction, diversion, dependency, tolerance, and hyperalgesia
History of alcoholism
Major psychological 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
Source: [97] *Table 9*

PATIENT RISK STRATIFICATION

Common to most clinical practice guidelines, and discussed in the FSMB 2017 Guidelines, is patient stratification by level of risk [113]. All practice guidelines for opioid analgesic prescribing recommend assessing the risk of misuse, abuse, or addiction in all patients before initiating long-term (≥90 days) opioid therapy and in high-risk patients prior to acute pain therapy. Patient risk level is designated as low, medium, or high based on background and clinical characteristics (***Table 9***) [97].

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 [21].

SAFETY PRECAUTIONS

A simplified approach to opioid prescribing safety, based on the core concept of universal precautions but designed with high specificity for opioid analgesics, was presented at the 2013 annual conference of the AAPM. The eight principles are specifically intended to reduce fatalities with opioid analgesic prescribing and are now incorporated in the AAPM Safe Opioid Prescribing Initiative [122]. They may be recalled using the acronym RELIABLE:

- **R**espiratory: If a patient on long-term opioids develops a respiratory condition (e.g., asthma, pneumonia, flu), reduce the opioid dose by 20% to 30%.

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- **E**xperience: Assess the patient before prescribing opioids to explore biologic, social, and psychiatric risk factors.
- **L**ong-term: Extended-release opioids should not be used for acute pain.
- **I**nitiating methadone: Never start methadone at a dose ≥15 mg/day.
- **A**pnea: Screen for hypoxemia and obstructive or central sleep apnea, especially in patients who are taking 150 mg/day MED or who are obese, infirm, or elderly.
- **B**enzodiazepines: Avoid these agents if possible because they enhance opioid toxicity.
- **L**ook for comorbidities: Patients often misuse opioid analgesics for their mental health disorder instead of their pain, so assess patients for a history of bipolar disorder, post-traumatic stress disorder, depression, stress, and general anxiety disorder.
- **E**xercise caution with rotation: Conversion tables and equal analgesic tables should not be used to determine opioid starting doses. Assume everyone is opioid naïve, start on a low dose, and titrate slowly to the maximum dose one can safely prescribe.

DEVELOPING A SAFE OPIOID TREATMENT PLAN FOR MANAGING CHRONIC PAIN

As discussed, healthcare professionals should know 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 pharmacologic or nonpharmacologic pain therapy without adequate pain relief are considered to be candidates for a trial of opioid therapy. The treatment plan should always be individualized for the patient and begun as an "initial therapeutic trial" before embarking on a definitive course of treatment [113].

All patients with pain have a level of risk that can only be roughly estimated initially and modified over time as more information is obtained. There are ten essential steps of opioid prescribing for chronic pain to help mitigate any potential problems [113]:

- Diagnosis with an appropriate differential
- Psychologic assessment, including risk of substance use disorders
- Informed consent
- Treatment agreement
- Pre- and post-treatment assessments of pain level and function
- Appropriate trial of opioid therapy with or without adjunctive medication
- Reassessment of patient levels of pain and functioning
- Regular assessment with the 5 A's (i.e., analgesia, activity, adverse effects, aberrant behaviors, and affect)
- Periodically review pain diagnosis and comorbid conditions, including substance use disorders
- Documentation

INFORMED CONSENT AND TREATMENT AGREEMENTS

The initial opioid prescription is preceded by a written informed consent or "treatment agreement" [113]. 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 [113].

The American Society of Interventional Pain Physicians asserts that a robust agreement, which is followed by all parties, is essential prior to initiating and maintaining opioid therapy, as such agreements reduce overuse, misuse, abuse, and diversion.

(https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed August 15, 2023.)

Level of Evidence: III (Evidence obtained from at least one relevant, high-quality nonrandomized trial or observational study with multiple moderate- or low-quality observational studies)

The treatment agreement also outlines joint prescriber and patient responsibilities [113]. The patient agrees to using medications safely, refraining from "doctor shopping," and consenting to routine urine drug tests (UDTs). The prescriber's responsibility is to address unforeseen problems and prescribe scheduled refills. Reasons for opioid therapy change or discontinuation should be listed [113]. Agreements can also include sections related to follow-up visits, monitoring, and safe storage and disposal of unused drugs.

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.

INITIATING A TRIAL OF OPIOID THERAPY

Opioid therapy should be presented as a trial for a pre-defined period (usually no more than 30 days). The goals of treatment should be reasonable improvements in pain, function, depression, anxiety, and avoidance of unnecessary or excessive medication use [113]. The treatment plan should describe therapy selection, measures of progress, and other diagnostic evaluations, consultations, referrals, and therapies.

In opioid-naïve patients, start at the lowest possible dose and titrate to effect. Dosages for opioid-tolerant patients should always be individualized and titrated by efficacy and tolerability [113]. 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 be knowledgeable of federal and state opioid prescribing regulations. Issues of equianalgesic dosing, close patient monitoring during all dose changes, and cross-tolerance with opioid conversion should be considered. If necessary, treatment may be augmented, with preference for nonopioid and immediate-release opioids over ER/LA opioids. Taper opioid dose when no longer needed [114].

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 [113]. This can include input from family members and/or the state prescription drug monitoring program (PDMP) [113]. 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 [10]:

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

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society of Interventional Pain Physicians recommends monitoring for side effects (e.g., constipation) and managing them appropriately, including discontinuation of opioids when indicated. (https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed August 15, 2023.)

Level of Evidence: I (Evidence obtained from multiple relevant high quality randomized controlled trials for effectiveness)

Assessment During Ongoing Opioid Therapy

Signs and symptoms that, if present, may suggest a problematic response to the opioid and interference with the goal of functional improvement include [123]:

- Excessive sleeping or days and nights turned around
- Diminished appetite
- Inability to concentrate or short attention span
- 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 [113]. 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.

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 [124; 125]:

- Verification: Is this a responsible opioid user?
- Identification: Is the identity of this patient verifiable?

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MONITORING FREQUENCY ACCORDING TO PATIENT RISK			
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	3 times per year	4 times per year
Source: [128]			*Table 10*

- **G**eneralization: Do we agree on mutual responsibilities and expectations?
- **I**nterpretation: Do I feel comfortable allowing this person to have controlled substances?
- **L**egalization: Am I acting legally and responsibly?

The foundation of VIGIL is a collaborative prescriber/pharmacist relationship [125; 126].

Current Opioid Misuse Measure

The Current Opioid Misuse Measure (COMM) is a 17-item patient self-report assessment designed to help clinicians identify misuse or abuse in patients with 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 [21]. 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

Guidelines by the 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 [127]. 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 [121].

Involvement of Family Members

Family members of the patient can provide 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 [123]:

- 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.
- Does the person smoke? Smoking increases pain and reduces the effectiveness of opioids. Smoking itself is an addictive behavior and, therefore, a clear risk for opioid addiction. If possible, opioids should be avoided persons who smoke.

Urine Drug Testing

UDTs may be used to monitor adherence to the prescribed treatment plan and to detect unsanctioned drug use [113]. They should be used more often in patients receiving addiction therapy, but clinical judgment is the ultimate guide to testing frequency (***Table 10***) [128]. High-quality evidence supporting the benefits of UDTs in improving patient care are lacking, as much of the existing evidence comes from industry-sponsored studies that can portray a biased perspective, usually by stressing the prevalence of aberrant behaviors in patients who then require more frequent UDT monitoring [129].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Society of Interventional Pain Physicians, presumptive urine drug testing should be implemented at initiation of opioid therapy, along with subsequent use as adherence monitoring, using in-office point of service testing, followed by confirmation with chromatography/mass spectrometry for accuracy in select cases, to identify patients who are noncompliant or abusing prescription drugs or illicit drugs. Urine drug testing may decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy.

(https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed August 15, 2023.)

Level of Evidence: III (Evidence obtained from at least one relevant, high-quality nonrandomized trial or observational study with multiple moderate- or low-quality observational studies)

Initially, testing involves the use of class-specific immunoassay drug panels [10]. 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 unless liquid chromatography is coupled with 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.

Ethical Concerns with UDTs

It is important to appreciate the limitations of UDTs. Healthcare providers are increasingly relying on UDTs as a means to reduce abuse and diversion of prescribed opioids. This has led to a proliferation in diagnostic laboratories that offer urine testing. With this increase have come questions of whether these business interests benefit or hinder patient care, what prescribers should do with the information they obtain, the accuracy of urine screens, and whether some companies and clinicians are financially exploiting the UDT boom [129]. A random sample of UDT results from 800 patients with pain treated at a Veterans Affairs facility found that 25.2% were negative for the prescribed opioid and 19.5% were positive for an illicit drug/unreported opioid [130]. However, a negative UDT result for the prescribed opioid does not necessarily indicate diversion; it may indicate the patient halted its use due to side effects, lack of efficacy, or pain remission. The increasingly stringent climate surrounding clinical decision-making regarding aberrant UDTs is concerning. In many cases, a negative result for the prescribed opioid or a positive UDT serves as the pretense to terminate a patient rather than an impetus to guide him or her into addiction treatment or an alternative pain management program [129].

In principle, and ideally in practice, UDTs are a worthwhile element of effective pain management and pharmacovigilance when used to enhance the diagnostic and therapeutic objectives of pain therapy. However, when UDT use is motivated by fear, coercion, or profiteering, patients may be offended or feel intimidated by the practice [129].

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 [24].

PATIENT AND CAREGIVER EDUCATION

Safe Use 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 ER/LA opioids, the FDA has developed a patient counseling document with information on the patient's specific medications, instructions for emergency situations and incomplete pain control, and warnings not to share medications or take them unless prescribed [114]. A copy of this form may be accessed online at https://www.fda.gov/media/86281/download.

When prescribing opioids, clinicians should provide patients with the following information and instructions [114]:

- Product-specific information
- Taking the opioid as prescribed
- Importance of dosing regimen adherence, managing missed doses, and prescriber contact if pain is not controlled

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- 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 (CNS) 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

Disposal of Opioids

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 [131]. According to the Office of National Drug Control Policy, 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 [132]. 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 [132]. Patients should be advised to flush prescription drugs down the toilet only if the label or accompanying patient information specifically instructs doing so.

The American College of Preventive Medicine has established the following best practices to avoid diversion of unused drugs and educate patients regarding drug disposal [131]:

- 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.

In April 2023, the FDA announced it will require manufacturers of opioid analgesics dispensed in outpatient settings to make prepaid mail-back envelopes available to outpatient pharmacies and other dispensers as an additional opioid analgesic disposal option for patients. The REMS modification also requires manufacturers to develop educational materials for patients on safe disposal of opioid analgesics, which outpatient pharmacies and other dispensers may provide to patients. The agency anticipates approval of the modified REMS in 2024 [133].

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 [113].

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 [113]. 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 [24].

MEDICAL RECORDS

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 [113]. 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.

DISCONTINUING OPIOID THERAPY

The decision to continue or end opioid prescribing should be based on a joint 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 [113].

Clinicians should provide physically dependent patients 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.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society of Interventional Pain Physicians recommends advising patients undergoing dosage titration in a trial of opioid therapy to avoid engaging in dangerous activities, such as driving a motor vehicle or the use of heavy machinery, until a stable dosage is established and it is certain that the opioid dose does not cause sedation, as well as when taking opioids with alcohol, benzodiazepines, or other sedating drugs.

(https://painphysicianjournal.com/current/pdf?article=NDIwMg%3D%3D&journal=103. Last accessed August 15, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

COMPLIANCE WITH FEDERAL AND STATE LAWS

OPIOID RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

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. Another element of opioid risk mitigation is FDA partnership 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 [123].

FDA AMENDMENTS ACT OF 2007

The FDA Amendments Act (FDAAA) of 2007 gave the FDA authority to require REMS from manufacturers to ensure that benefits of a drug or biological product outweigh risks. REMS replaced the previously existing risk management programs, termed Risk Minimization Action Plans (RiskMAPs). An important distinction between the two programs is that the FDA did not have authority to require or enforce a RiskMAP after product approval. The FDA now has the authority to require REMS as part of the approval process for a new medication or post-approval if the agency becomes aware of new safety information pertaining to serious medication-associated risks following approval for marketing [114].

As defined by the FDAAA, REMS may include a medication guide, a patient education package insert, a communication plan, and other elements to assure safe use (ETASUs). ETASUs must address the goals to mitigate a specific serious risk listed in the labeling of the drug and may include [114]:

- Prescriber training, experience, or certification
- Distributor or dispenser training or certification
- Restricted distribution or dispensing
- Dispensing limited to patients with evidence of safe use conditions, such as laboratory test results
- Patient monitoring
- Patient enrollment in a registry
- Physician and/or pharmacist enrollment in a registry

The FDA maintains a list of current opioid analgesic REMS at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm [134].

SPECIFIC OPIOIDS WITH A REMS REQUIREMENT

In 2011, the FDA announced the components of REMS that would apply to all ER/LA opioid formulations. The decision to not include short-acting formulations was based on the substantially greater opioid amount in ER/LA formulations and the corresponding greater risk of serious adverse outcomes, including fatality, when taken by someone for whom they were not prescribed, by patients who succeed in defeating the delayed-release mechanism, or by any user co-ingesting alcohol, benzodiazepines, or other respiratory suppressant substances. Primary elements of the ER/LA REMS include changes in product labeling and the requirement that all ER/LA opioid formulation manufacturers provide specific information to prescribers and patients [135]. For example, there is a new indication for all ER/LA opioids that the pain must be severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. The original indication for the treatment of "moderate" pain was eliminated. In addition, the distinctions between cancer pain and chronic noncancer pain were removed. Prescriber education regarding ER/LA opioids is provided through accredited continuing education activities supported by independent

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ADVANTAGES AND DISADVANTAGES OF ADF STRATEGIES		
ADF Strategy	**Advantages**	**Disadvantages**
Physical barriers	Prevents crushing or chewing to block rapid high-dose opioid release into the system Prevents accidental crushing or chewing in compliant patients No adverse events in compliant patients FDA-approved formulation available	Does not deter abuse of intact tablets Only one FDA-approved product available
Aversive components (e.g., niacin)	May prevent abuse by chewing or crushing the product May limit abuse of intact tablets because taking too much will amplify adverse events	Potential adverse events in compliant patients taking product as intended Adverse events with intact tablets may prevent legitimate dose increase if pain increases or efficacy decreases over time Adverse events may not be sufficient to deter a motivated abuser No FDA-approved formulations
Sequestered antagonist (e.g., naloxone, naltrexone)	Prevents abuse by chewing or crushing opioids FDA-approved formulation available	Does not deter abuse of intact tablets Chewing or crushing the tablet may trigger severe withdrawal symptoms
New molecular entities/ prodrugs	Prevents abuse by providing a chemical barrier to the in vitro conversion to the parent opioid.	—

Source: [138; 144] *Table 11*

educational grants from ER/LA opioid analgesic companies. This includes guidance regarding patient education on the risks and benefits of ER/LA opioid analgesics [135].

In 2012, the FDA issued a class-specific REMS for all transmucosal immediate-release fentanyl (TIRF) opioid products. Training was required for all prescribers, pharmacies, distributors, and outpatients who prescribed, dispensed, or received TIRF products [136]. In December 2020, the FDA approved modifications to this REMS. The modified TIRF REMS consists of a restricted distribution program to ensure the safe use of TIRF medicines, including use only in opioid-tolerant patients [136]. The modified REMS requires that prescribers document a patient's opioid tolerance; that outpatient pharmacies dispensing TIRF medicines document and verify a patient's opioid tolerance prior to dispensing; that inpatient pharmacies develop internal policies to verify opioid tolerance in patients who require TIRF medicines while hospitalized; and that a new patient registry be established to monitor accidental exposure, misuse, abuse, addiction, and overdose [136].

ABUSE-DETERRENT OPIOID FORMULATIONS

Drug developers, manufacturers, and regulatory bodies face daunting challenges in formulating and implementing strategies to reduce the abuse, addiction, diversion, and overdose of prescription opioids. One challenge has been to identify and manufacture analgesics effective in the treatment of severe pain that also possess minimal abuse liability. These products must provide full analgesia with low "opioid attractiveness" to persons intent on abusing or diverting the drug; this strategy is consistent with the opioid REMS principle of drug benefit outweighing risk [137]. The development of abuse-deterrent formulations (ADFs) was also an approach to help avoid the unintended harms to patients with legitimate pain observed in Washington and Florida, where imposition of opioid prescribing restrictions were found to discourage legitimate treatment of chronic pain while making little or no impact on opioid analgesic abuse and diversion [138]. Although ADF opioids retain some abuse liability if used inappropriately or combined with other substances, most ADFs are now being developed to prevent defeat of the delayed-release mechanism or use through illicit routes of administration [139; 140].

Helping to prompt the development of ADF opioids were reports that as many as 80% of prescription opioid abusers in drug rehabilitation tampered with ER opioid formulations [141]. Strategies used by opioid abusers to disable the delayed-release mechanism to accelerate drug release include crushing and swallowing; crushing and snorting; crushing and smoking; or crushing, dissolving, and injecting. The FDA states that ADFs should target known or expected routes of abuse for the opioid constituent in the given formulation [142].

ADVANTAGES AND DISADVANTAGES OF DIFFERENT ADF STRATEGIES

Several ADF opioids have received approval for marketing in the United States; others are in the process of evaluation, and one ADF was released for marketing and subsequently recalled by the manufacturer [138; 143]. These formulations use different strategies to prevent misuse, with varying advantages and disadvantages (***Table 11***) [138].

While all ADF strategies may potentially deter tampering, physical barriers to crushing or chewing appear to be the only strategy that benefits nonabusers and abusers alike by preventing accidental crushing or chewing and not inducing adverse events. This contrasts with strategies that precipitate adverse events to deter inappropriate use, such as ADFs that use sequestered aversive agents that will induce adverse events in patients who chew or crush the tablets, accidentally or without intent of abuse. The extent of deterrence from these formulations is unclear because some persons are willing to endure discomfort from the aversive agent in order to obtain the more intense high from tampering. Sequestered opioid antagonists may offer a more effective approach in pharmacologic abuse deterrence by rendering the opioid ineffective, but they can induce sudden and severe opioid withdrawal in physically dependent patients who accidentally chew the tablet [138].

ADF OUTCOME DATA

Although opioid ADFs have been introduced into widespread clinical use relatively recently, several studies of their efficacy have already been published. These reports have documented significantly reduced abuse rates of ADF opioids after they have fully replaced the original formulations, but no effect on the overall rates of opioid abuse. For example, data were obtained on 140,496 persons assessed for substance abuse treatment, spanning from one year before ADF OxyContin (Oxy ADF) introduction to two years post-Oxy ADF introduction. Abuse of OxyContin was 41% lower with the ADF versus the original formulation, including a 17% decrease in oral abuse and a 66% decrease in abuse through non-oral routes. Meaningful reductions in ER morphine and ER oxymorphone abuse rates were not found. The authors concluded that conversion of OxyContin to an ADF formulation was successful in reducing non-oral administration that requires tampering [145]. Another study found that following OxyContin ADF introduction, poison center exposures for oxycodone ER abuse declined 38% per population and 32% per unique recipients of dispensed drug. Therapeutic error exposures declined 24% per population and 15% per unique recipients of dispensed drug, and diversion reports declined 53% per population and 50% per unique recipients of dispensed drug. The declines were greater than those observed for other prescription opioids in aggregate [146]. However, several published reports have documented the abandonment of opioid analgesics and a migration to heroin use by previous OxyContin abusers following the introduction of ADF OxyContin [147; 148].

REGULATORY MANDATES

The FDA has prohibited labeling or marketing claims of abuse resistance or abuse deterrence to be used in any ADF opioid product because supportive epidemiologic data have not yet been published [149]. Any future label claim of abuse deterrence must be supported by post-marketing data [138].

In 2013, Purdue Pharma and Endo Pharma, the makers of OxyContin and Opana ER, respectively, requested a ruling from the FDA that the original formulations were removed from market and replaced by ADFs because of safety or efficacy concerns. Such a ruling would render the original formulations ineligible for generic replication, thus protecting ADF OxyContin and Opana ER market share from generic non-ADF competition [150]. The FDA ruled in favor of this request for Purdue but not for Endo. The basis for the decision was the extent of abuse liability with the original OxyContin preparation and insufficiency in the abuse deterrence with the ADF formulation to block future applications to produce generic versions of the non-ADF Opana ER [151]. Interestingly, this favorable ruling for Purdue Pharma was made on April 16, 2013, the exact date of patent expiration for OxyContin [150].

In 2013, the FDA issued a draft document to guide pharmaceutical companies in developing ADF opioid products. Although the FDA strongly encourages industry to employ ADFs in new opioid products, the guidance document fell short of a mandate [142]. Later that year, the FDA approved an ER formulation of hydrocodone (Zohydro) that lacks abuse-deterrent properties, which seemed contradictory to the FDA stance on ADF product development [152].

In June 2017, the FDA requested that Endo Pharma remove the reformulated Opana ER from the market based on concerns that the benefits of the drug may no longer outweigh the risks [153]. This is the first time the FDA has taken steps to remove a currently marketed opioid pain medication. The agency's decision was based on a review of available postmarketing data, which demonstrated a significant shift in the route of abuse of Opana ER from nasal to injection following release of the ADF formulation. Injection abuse of reformulated Opana ER has been associated with a serious outbreak of HIV and hepatitis C and with cases of thrombotic microangiopathy [153].

OTHER GOVERNMENT AND INDUSTRY EFFORTS

In response to increasing rates of opioid analgesic abuse, addiction, diversion, and overdose, the National Drug Control Policy created a multiagency Drug Abuse Prevention Plan in 2011 to reduce prescription drug abuse. The four key elements of the plan are expansion of PDMPs; responsible disposal of unused medications; reduction of pill mills through enhanced law enforcement efforts; and support for provider and patient education. Regarding provider education, several state medical

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boards (e.g., California, West Virginia) require prescribers to obtain continuing education credit in pain management and prescription opioid use [154].

As noted, emerging trends and patterns of prescription opioid abuse, addiction, and overdose are monitored by several industry and government agencies through data collection from a variety of sources, including health insurance claims; the Automation of Reports and Consolidated Orders System (ARCOS), a DEA-run program that monitors the flow of controlled substances from manufacturing through distribution to retail sale or dispensing; the Treatment Episode Data Set (TEDS), which monitors treatment admissions; National Center for Health Statistics state mortality data; and the Researched, Abuse, Diversion and Addiction-Related Surveillance (RADARS) System, which monitors prescription drug abuse, misuse, and diversion [155].

The DEA is responsible for formulating federal standards for the handling of controlled substances. In 2011, the DEA began requiring every state to implement electronic databases that track prescribing habits, referred to as PDMPs. Specific policies regarding controlled substances are administered at the state level [156].

Almost all states have enacted PDMPs to facilitate the collection, analysis, and reporting of information on controlled substances prescribing and dispensing. Most PDMPs employ electronic data transfer systems that transmit prescription information from the dispensing pharmacy to a state agency [113].

The General Accounting Office evaluated the efficacy of PDMPs and concluded that such programs have the potential to help law enforcement and regulatory agencies rapidly identify and investigate activities that may involve illegal prescribing, dispensing, or consumption of controlled substances. In states that have made real-time data available, PDMPs can help reduce prescription drug abuse and diversion by allowing prescribers to access and detect whether a patient has been receiving multiple prescriptions for controlled substances or whether a patient has filled or refilled an order for a prescribed opioid [113]. However, several concerns over PDMPs were voiced around the time of their widespread introduction, including the risk that PDMPs may negatively affect patients with legitimate opioid need by reducing opioid prescribing, potential privacy issues, and more frequent physician visits [156].

REGULATIONS AND PROGRAMS AT THE STATE LEVEL

Several regulations and programs at the state level have been enacted in an effort to reduce prescription opioid abuse, diversion, and overdose, including [157]:

- 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

UNINTENDED NEGATIVE CONSEQUENCES OF EFFORTS TO REDUCE PRESCRIBED OPIOID MISUSE, DIVERSION, AND OVERDOSE

The United States is unquestionably experiencing serious substance abuse problems involving prescription opioids. Although efforts to curtail opioid analgesic prescribing and distribution have been well intentioned, several of the approaches have resulted in unintended consequences.

DIFFICULTY OBTAINING LEGITIMATE OPIOID ANALGESICS

Enactments of restrictive mandates to govern opioid analgesic prescribing and dispensing have created difficulty for patients in accessing legitimate opioid therapeutics. This has been especially well documented in the state of Washington, but it is highly prevalent in general. Concerns have been voiced by numerous key opinion leaders and prominent individuals in the pain treatment profession and community in an effort to draw attention to regulatory and law enforcement overreach at the expense of patients suffering in pain who require access to opioid analgesics.

One example is Jan Chambers, president of the National Fibromyalgia and Chronic Pain Association (NFMCPA). For incorporation into a position paper on patient rights to access pain medication, Chambers sought input from members requiring prescribed opioids for their pain condition. In the open letter encouraging member input, Chambers expressed concern over federal law enforcement and regulatory overreach involving heightened scrutiny of prescription filing and dispensing. Mandates cited as especially harmful were patient-prescriber opioid contracts required to specify a single pharmacy, a 30-day maximum supply of opioids and no refills, and prohibition of faxing or phoning opioid prescriptions to a pharmacy. Also mentioned was the increasing rate of pharmacy refusal to dispense opioids, the result of greater pressures imposed by the DEA on pharmacy networks to obtain additional patient information to verify legitimacy. These pharmacy networks, in turn, have transferred this burden to individual pharmacists, who, similar to prescribers, have become fearful of attracting DEA scrutiny over opioid prescription dispensing. The end result has been difficulty finding a pharmacy to fill opioid prescriptions [158].

Similar concerns over negative unintended patient impact were communicated by Amy Abernethy, president of the American Academy of Hospice and Palliative Medicine (AAHPM) to the National Conference of Insurance Legislators (NCOIL). NCOIL is an organization of state legislators involved in insurance legislation and regulation, and her response concerned several recommendations in a proposed set of best practices guidelines to reduce opioid abuse that were released by NCOIL in 2013. Strategies included in the NCOIL draft were those already implemented at the state level that led to measurable reductions in abuse and overdose. Abernethy countered by arguing that the narrow measure of success came at the expense of patients and providers [159].

With a shortage of pain medicine specialists in the United States, most chronic pain care is provided at the primary care level, and in some states (e.g., Washington), many primary care practices display signs in offices stating they no longer prescribe opioids. Interestingly, a small number of primary care physicians have chosen to transform their practices into cash-only entities and charge very high fees for what amounts to the sole prescribing of opioid analgesics. Patients requiring opioids to maintain pain control and quality of life are forced to seek treatment from these physicians because many others have become intimidated by the new legislation [5].

PATIENTS WHO REQUIRE ULTRA-HIGH-DOSE OPIOIDS

An element of the backlash against escalating opioid prescribing and associated problems has been intense lobbying by some pain professionals to impose pre-established dose ceiling on opioid prescribing, such that a maximum daily dosage cannot be exceeded. Prominent among these groups has been Physicians for Responsible Opioid Prescribing (PROP) and the advocacy group Public Citizen. The imposition of a 100-mg MED maximum daily ceiling and a maximum prescribing duration of 90 consecutive days was requested for noncancer pain. The groups cited observational study findings of a correlational relationship between prescribed opioid dose and overdose risk as evidence, but these recommendations were rejected by the FDA [160].

Despite FDA rejection of a mandate for daily dose ceilings, many practitioners believe that high-dose prescribing is irresponsible and without medical legitimacy. This view was disseminated and seemingly legitimized by the 2009 opioid prescribing guidelines published by the APS and the AAPM, which stated that no existing evidence supports daily opioid doses ≥200 mg MED [115]. The validity of these assertions has been undermined by several findings of differences between patients in the opioid dose necessary to achieve sufficient pain control, which can vary 40-fold for the same clinical condition [161]. While ultra-high-dose opioid prescribing remains controversial, a small subset of patients do require massive doses of opioids for chronic pain. Authors and guidelines statements of the contrary are based on opinion without empirical support [162].

Patients with chronic pain who require ultra-high-dose opioids, in some cases more than 2,000 mg/day MED, are likely to be labeled as addicts or abusers by healthcare professionals and family members alike. In general, these patients are profoundly ill, impaired, and/or bed- or house-bound due to severe unremitting pain refractory to analgesic efforts using lower-dose opioids. The reason some patients require ultra-high opioid doses remains unclear, but it is very likely that some, and perhaps the majority, possess a cytochrome P450 polymorphism or other genetic abnormality [163].

Patients with chronic pain who legitimately require ultra-high-dose opioids also require supplemental management considerations in addition to those applied to all patients with chronic pain prescribed opioids. Patients and their caregivers should receive education on recognizing overmedication and overdose and what to do if these occur, especially before tolerance has developed. Patients should be restricted from use of benzodiazepines, muscle relaxants, sedatives, and any other potential respiratory depressant medication. While not used in most pain medicine settings, blood levels of opioids have value when a significant discrepancy is observed between prescribed dose and apparent drug effect; serum level results can suggest metabolic variation that impacts opioid dose-response. Serum opioid level testing in these patients can also establish baseline for comparison against future tests. In the unfortunate event of patient death while receiving ultra-high-dose opioids, documenting high serum opioid level while the patient was ambulatory and functional can defend the prescriber against accusation of responsibility for the patient's overdose death when coroner findings reveal high serum opioid levels in the absence of other explanatory findings [162].

Some complications are highly probable with ultra-high-dose opioid therapy that may not occur with lower doses. Endocrine suppression is likely to occur, with testosterone suppression possible in men and some women. Sudden suppression of adrenal corticoids in an opioid-maintained patient manifests in nausea, weakness, and a drop in blood pressure. For these patients, hormone replacement is necessary if opioids remain essential for pain control. Movement and physical exercises are strongly recommended. Almost without exception, patients who require ultra-high opioid dosages have been too ill to engage in normal social or family functions and usually require resocialization counseling for guidance and motivation to resocialize and begin a new quality of life [162].

LAW ENFORCEMENT TACTICS

Activities by the DEA to curb prescription opioid abuse and diversion have been identified in particular as potentially excessive and inappropriate. The U.S. Congress has pressured the DEA to reduce the diversion of prescribed opioids, which the DEA initially achieved through the successful raiding and closure of many pill mills and rogue Internet pharmacies. The focus of the agency has now shifted to reducing opioid supply by targeting wholesalers and pharmacies within the legitimate supply chain. Many complaints have centered on DEA use of

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tactics identical to those use in combating illegal drug cartels, such as wiretaps, undercover operations, and informants. Retail and wholesale pharmacies raided by DEA tactical squads have complained of being treated as if they were armed criminal organizations [164].

The DEA has accelerated the use of audits and inspections to identify and sanction drug wholesalers, levying millions of dollars in fines for what it has claimed were violations of the law. In 2012, the DEA suspended the license of drug wholesaler Cardinal Health, Inc., prohibiting opioid analgesic sales from its central Florida center. The DEA rationale was failure to detect suspicious order volume from several of Cardinal Health's pharmacy customers. Numerous Walgreens and CVS pharmacies and distribution centers were also raided [164].

The DEA has justified their tactics on the basis of Congressional pressure to contain opioid diversion, with agency success measured by disruption and destruction of organizations and networks feeding the problem. However, John Burke, president of the nonprofit National Association of Drug Diversion Investigators (NADDI), stated that DEA behavior reflects a mindset that retail and wholesale pharmacies comprise an enemy requiring containment. Concerns have been raised over the potential of DEA activity to adversely and negatively impact legitimate medical practice. This has led several congressional members to request that the Government Accountability Office investigate the effect of DEA conduct on medication shortages for patients with pain [164].

Actions of the DEA have produced widespread fear among prescribers and retail pharmacists regarding the prescribing or dispensing of opioids. In some localities, pharmacists greatly restrict dispensing opioids by refusing to fill prescriptions paid for in cash, from customers not well known to them, or from customers from certain geographic areas. Other pharmacy chains have stopped filling opioid prescriptions from higher-volume opioid prescribers. Prescribers report feeling burdened by mandates to tighten patient monitoring by increasing UDTs, documentation, and pill counts [164].

The DEA is also tasked with the oversight and control of ingredients allocated to drug manufacturers for drug production that are deemed an abuse liability. This task is performed annually and is based on manufacturer projection of legitimate patient needs. Manufacturers of drug products with abuse liability complain of DEA failure to authorize sufficient materials for adequate customer supply, which the DEA defends as resulting from poor business decisions by the manufacturers. This has contributed to patient inability to access needed prescribed opioids [164].

INCREASE IN HEROIN USE

Of great concern is the likelihood that persons addicted to prescription opioids will switch to heroin if their preferred opioid becomes difficult to obtain or extract from ADF opioid preparations. Some experts predicted a resurgence of heroin abuse and fatal overdose, largely driven by opioid analgesic prescribing restrictions and by replacement of some opioid preparations by ADFs [165; 166; 167].

Statistics seem to bear this out. In 2014, the percentage of prescription opioid abuse was lower than the percentages in most years from 2002 to 2012 (although similar to the percentage in 2013) [167]. At the same time, heroin use increased. In 2014, the estimates of both current and past heroin use were higher than the estimates for most years between 2002 and 2013 [168]. In addition, first-time past-year use nearly doubled between 2006 and 2012 [169]. Heroin use continued to increase in 2021 [170]. Past-year heroin initiation rose sharply in all regions in the United States, except the South. Unfortunately, the data do not provide estimates of patients with chronic pain resorting to heroin use when their opioid analgesic prescriptions are decreased or discontinued.

One study examined the impact of ADF OxyContin introduction on the abuse of OxyContin and other opioids. Researchers analyzed the results of surveys given to 2,566 patients entering treatment for opioid addiction between July 2009 and March 2012, before and after the 2010 introduction of ADF OxyContin [171]. During the 21-month post-ADF period, endorsement of hydrocodone or oxycodone agents other than OxyContin as the preferred opioid changed little from before ADF introduction, but endorsement of high-potency fentanyl or hydromorphone as the preferred opioid rose from 20.1% to 32.3%. Of opioids used in the past 30 days to get high, OxyContin fell from 47.4% to 30%, while heroin nearly doubled. More detailed questioning of 103 abusing patients found unanimous preference for the old OxyContin formulation, and 66% of those preferring pre-ADF OxyContin switched to another opioid, most commonly heroin. This switch appeared to be causally linked. No evidence suggested that OxyContin abusers quit using opioids as the result of ADF introduction; instead, they shifted their drug of choice to other opioids, primarily heroin. The authors concluded that ADF OxyContin successfully reduced OxyContin abuse, but also led to increased abuse of replacement opioids [171].

Analysis of data from the National Poison Data System, which covers the reporting from all U.S. poison centers, indicated that, in the period after ADF OxyContin introduction, abuse exposures decreased 36% for ADF OxyContin, increased 20% for other single-entity oxycodone, and increased 42% for heroin. Accidental opioid exposures decreased 39% for ADF OxyContin, increased 21% for heroin, and remained unchanged for other single-entity oxycodone products. The authors conclude that opioid analgesic ADFs can reduce abuse of the specific opioid product but may also lead to switching to other accessible non-ADF opioids [172].

Thus, the introduction of ADF opioids has driven a movement away from prescription opioids and to heroin and has increased the illicit price of traditional non-ADF opioids as they are phased out of the supply chain. During this abandonment by abusers and addicts of the precisely measured amount of pure drug in prescription opioids for the illicit street market of drug

dealers, needles, and kitchen table chemists, public health officials and law enforcement agencies are noting increases in heroin overdoses, crime, and other public health problems [173]. These unanticipated negative consequences provide a compelling reminder that societal problems of substance abuse and addiction are complex and multifaceted. Simplistic solutions seeking only to restrict drug supply have never succeeded in reducing drug demand.

INCREASINGLY RESTRICTED ACCESS TO THERAPIES FOR OPIOID ADDICTION

Restricted access to opioid analgesics is also negatively impacting patients attempting to access treatment for opioid addiction. The opioid analgesics methadone and buprenorphine comprise the backbone of outpatient multidisciplinary treatment of opioid addiction in the United States. A 2013 press release by the ASAM states that investigation into state Medicaid and private insurance coverage found increasing restrictions due to policy changes over coverage, daily dose, prior authorizations, and the requirement of previous failed treatment approaches. The end result of these imposed barriers to accessing opioid addiction medications is an increase in patient denial of services, which ASAM states is senseless and unethical considering the epidemic-level rates of opioid addiction and overdose deaths [174].

PATIENT TERMINATION

Several clinical practice guidelines for safe opioid prescribing explicitly endorse patient termination in the event of abnormal UDT results, aberrant drug-related behaviors, other violations of the patient-provider contract, or deterioration in the provider-patient relationship [97]. This approach is controversial, and as stated by Ballantyne, "The surest way to hurt patients (and society) is to abandon them when they deviate from the constructive relationship envisaged by the treating practitioner, only to trail from physician to physician to obtain the drug they need, or worse still, seek illicit supplies" [175].

Clinician response to aberrant behaviors should involve an assessment of seriousness, underlying cause, likelihood of recurrence, and clinical context of the aberrant behavior [115]. Occasional episodes of non-serious violations can be managed by patient education and enhanced monitoring [176]. The basis of opioid analgesic termination should be consistent with those for any other medication class, where discontinuation is prompted when opioid therapy benefits are outweighed by harms. Reasons given for termination include [177]:

- Opioids are no longer effective.
- Opioids no longer stabilize the patient or improve function.
- Patient has lost control over his or her use of the opioid.
- Patient is diverting drugs.
- Patient is not able to stop using alcohol, benzodiazepines, or other CNS depressants.
- Adverse effects become unmanageable.

PATIENTS WITH CHRONIC PAIN AND SUBSTANCE USE DISORDER

Alcohol, street drugs, and prescription medications are used by patients with chronic pain for diverse reasons, including the self-medication of pain, insomnia, depression or anxiety, or intrusive trauma memories; as recreation with occasional use; as a compulsive act driven by addiction; and to avoid withdrawal symptoms [178]. Chronic pain and substance use disorder often coexist, and each condition is a risk factor for the other. Whenever possible, active substance abuse disorder in patients with chronic pain should be treated because of safety concerns and because active substance use disorder interferes with the therapeutic progress in the pain condition due to overlapping mechanisms. Active addiction augments pain stimuli processing and perception through alterations in the input, processing, and modulation of nociceptive stimuli, sympathetic activation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and opioid tolerance (in active opioid addiction). Persons with addiction have reduced pain tolerance and increased pain perception, the result of baseline perceptual pathway reorganization from the interactive effects of both conditions [20].

Some personality traits common in patients with addiction, such as external locus of control and catastrophization, are predictors of poor outcome in pain therapy. Intoxication and withdrawal activate the sympathetic nervous system to augment pain perception and increase muscle tension, irritability, and anxiety. The depletion of brain dopamine associated with withdrawal exacerbates discomfort in addicted patients. Many patients with addiction have lost their network of social support, another factor associated with poor pain therapy outcome [20].

In susceptible persons with chronic pain, use of opioid analgesics for pain relief can lead to a cyclical relationship between pain symptoms, opioid use, and drug effect that is driven by positive and negative reinforcement. The positive reinforcement from opioids comes from induction of a pleasurable state such as euphoria or relaxation, with negative reinforcement coming from elimination of an unpleasant state such as pain or distress. In some patients with chronic pain and biopsychosocial risk factors for addiction, the reinforcing effects they experience from opioids are sufficiently powerful to compel compulsive efforts to replicate the drug experience. Chronic pain adds a layer of complexity to the development and management of opioid addiction. The positive and negative effects of opioids become more elusive over time, and tolerance develops to the analgesic effect. Attempts to cut back or quit can induce opioid withdrawal or the unmasking of severe pain. The patient becomes increasingly preoccupied with obtaining and using opioid analgesics to alleviate his or her intense physical and emotional distress. This preoccupation can be severe, to the point of involving the entirety of motivational resources. Although patients with chronic pain

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and opioid use disorder represent a complex and challenging population, these chronic co-occurring conditions can be effectively managed [177].

Some people have achieved durable recovery from their substance use disorder and also require medical care for long-standing pain or pain that developed and became chronic during their recovery. Although the former drug of choice is the agent most likely to lead to cravings and relapse, those with a history of addiction to any drug (or alcohol) are susceptible to developing an opioid use disorder in the context of pain treatment. It is important to note that among patients in recovery from a substance abuse disorder, risk of developing problematic opioid analgesic use is inversely proportional to their duration of recovery. While many patients with a previously active substance use disorder are forthcoming during the comprehensive assessment, some may not be; others may lack an appreciation of either the gravity of their former substance abuse disorder or the clinical importance in disclosing this history to their healthcare provider. Family members can be a valuable resource in providing this information [177].

It is important for the prescriber to determine the recovery status of the patient in order to appropriately tailor the treatment plan. For patients who have achieved stable remission, corroborate and support them in their recovery. If a patient is receiving buprenorphine or methadone maintenance therapy for an opioid use disorder, verify and continue buprenorphine or methadone. If a patient has an active substance abuse disorder, refer him or her to a substance abuse specialist, if possible, for further evaluation [127; 177].

An important point is that clinicians often find patients with chronic pain to be difficult to treat, due to the pain condition often eluding diagnosis and the effects unrelenting pain can have on patient ability to interact calmly and civilly. A comorbid substance abuse disorder amplifies the likelihood of difficult behavior from the patient. Such patients can provoke strong negative responses from treatment providers, often based on either frustration from attempting to treat difficult or intractable problems or clinicians feeling they are working harder for the well-being of the patient than the patient is. It may be helpful for clinicians to remind themselves that, despite the apparent lack of patient motivation, no one would wish the experience of comorbid pain and addiction on anyone [177].

These patients have complex and intense needs, best served by a treatment team approach involving a team of professionals, including [179]:

- Primary care provider
- Addiction specialist
- Pain specialist
- Nurse
- Pharmacist
- Psychiatrist
- Psychologist
- Other behavioral health specialists, such as social workers or marriage and family therapists
- Physical or occupational therapists

To help build a therapeutic relationship with the patient, the following approach is suggested [177]:

- Listen actively.
- Ask open-ended, nonjudgmental questions.
- Restate patient accounts to make sure they have been understood.
- Use clarifying statements (e.g., "It sounds as if the pain is worse than usual this week").
- Demonstrate empathy. One approach is to acknowledge the effort required to simply get through each day with constant pain.
- Use feeling statements (e.g., "This must be very difficult for you").

Referral to an addiction professional for further substance abuse disorder evaluation and possible treatment does not negate patient need for pain treatment, because addiction treatment programs rarely have the resources or expertise to treat pain. Patients who are seeking treatment for chronic pain with an unacknowledged substance abuse disorder may react negatively when told of their referral to an addiction professional. The clinician-patient relationship is especially critical for patients who have comorbid pain and substance abuse disorders. They may anticipate clinician criticism or judgment of their substance use, dismissal of their pain complaints, or misinterpret concern over a possible substance abuse disorder as lack of concern for their pain. They may blame themselves for the substance abuse problem and expect their healthcare provider to respond in kind. Clinicians should convey respect and concern and reassure patients they fully understand the pain and the substance abuse disorder are uninvited chronic illnesses requiring concurrent treatment. It is important to clearly explain the purpose of the referral, with the following approach suggested [177]:

- Present the substance abuse disorder referral as you would to any other specialist, using a matter-of-fact and unapologetic tone.
- Emphasize the importance of assessing all factors, including substance abuse disorders, that may be contributing to chronic pain and that ongoing problems with substance abuse can interfere with optimal treatment of chronic pain.
- Avoid focusing on patient explanations of their substance use.
- Reassure patients that further evaluation and possible treatment of their substance abuse problem does not mean abandonment by their healthcare provider or neglect of their chronic pain condition. Emphasize that their care will be coordinated among all involved professionals.

- Reassure the patient that federal regulations hold clinicians to a high standard of confidentiality concerning patient drug and alcohol treatment information.

TREATMENT OF SUBSTANCE USE DISORDER

Not infrequently, primary care providers do not have access to specialized addiction professionals or programs for patient referral. Although coexisting pain and addiction rank among the most challenging conditions to manage in primary care, recovery is possible. Providers should practice patience, flexibility, and consistent motivational support with the patient. When addiction specialists are lacking, clinicians should [178]:

- Identify contributory factors to the chronic pain and use of substances
- Encourage and support the patient in developing a self-care program
- Implement or refer to initiate active treatment of the various underlying factors
- Provide regular patient follow-up to monitor self-care and treatments and to revise the plan, as needed

The goals of treatment include avoiding harmful use of substances and achieving physical, psychological, and spiritual well-being. In patients with chronic pain with substance abuse disorders, there is a degree of overlap when substance abuse disorder treatment involves a biopsychosocial approach, as it ideally does. Effective approaches for substance abuse disorder include a combination of [178]:

- Cognitive-behavioral therapy that addresses addiction recovery and chronic pain
- Deep relaxation/meditation through mindfulness, progressive muscle relaxation, and/or other approaches
- Working with an addiction counselor to explore substance use issues and to support recovery
- 12-step program involvement, through Alcoholics Anonymous (AA), Narcotics Anonymous (NA), or Methadone Anonymous (MA), when appropriate. Every 12-step program has sponsors who are support persons successful in their recovery through their respective 12-step program, with a desire to work with new members to help them achieve recovery success. The patient should be encouraged to find a sponsor.
- Alternatives to 12-step programs for peer support in substance abuse recovery (e.g., Smart Recovery and Rational Recovery)
- Chronic Pain Anonymous, the peer-support program for those with chronic pain

Treatment of Opioid Use Disorder in Patients with Chronic Pain

For patients on chronic opioid therapy who have minor opioid abuse relapses but quickly regain stability, involving substance abuse counseling in the medical setting or through a formal addiction program may suffice. One problem is that many addiction treatment programs will not admit patients who require the ongoing use of opioid analgesics for pain. In patients whose frequent relapses indicate a serious opioid use disorder, the best option may be referral to an opioid treatment program for methadone therapy or initiation of buprenorphine [177]. Methadone and buprenorphine can be used in patients with opioid use disorder during detoxification. With this approach, the patient is slowly transitioned from the dose of their illicit opioid to an opioid-free state by switching the illicit opioid to the withdrawal medication and slowly decreasing the detoxification medication dose. However, in the context of treating the opioid use disorder, the patient is placed on methadone or buprenorphine for an extended period. Formerly termed "maintenance therapy," this is now called "medication-assisted treatment" [180].

Treatment of opioid addiction with methadone or buprenorphine is intended to stabilize dysregulated brain pathways, thereby reducing craving and relapse risk. Persons with opioid addiction remain at very high risk of opioid relapse after successful detoxification and cessation of acute opioid withdrawal symptoms. Profound changes in brain function that occur with the development and progression of opioid addiction become unmasked with cessation of opioid use. Factors contributing to relapse vulnerability in persons attempting recovery from opioid addiction include craving for opioids, hypersensitivity to emotional stress, an inability to experience pleasure or reward, and a persistent state of distress, anxiety, or malaise [181]. For many patients with opioid addiction, treatment should address these alterations in neurobiology. By targeting the same brain receptors and pathways as the abused opioid, pharmacotherapy with opioid agonists or partial agonists can effectively manage opioid withdrawal symptoms and play an essential part in the ongoing treatment plan [182]. Methadone and buprenorphine are the two most widely used and effective pharmacotherapies for opioid use disorder, and both have regulatory approval in the United States for this indication [183]. Naltrexone is also approved for treatment of opioid use disorder [99; 182]. In 2018, the FDA approved the first non-opioid for the management of opioid withdrawal symptoms [184]. Lofexidine may be used for up to 14 days to lessen the severity of symptoms of opioid withdrawal as part of a long-term treatment plan [99].

Methadone Therapy

Methadone has been in clinical use since 1965 as a treatment for opioid addiction. Its use is based on the principle that a long-acting mu opioid agonist at a sufficient dose prevents opioid withdrawal, blocks the desired effects if other opioid drugs are abused, and diminishes the craving for opioids [185].

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A network of opioid treatment program regulatory and dispensing systems has been implemented to dispense methadone for opioid addiction, where the patient is administered methadone once a day under staff observation. Some stabilized patients are allowed up to a 30-day supply of take-home methadone, depending on their length of maintenance and compliance with other opioid treatment program rules. However, for some opioid-dependent persons, this system is not feasible due to lack of proximity to an opioid treatment program, a schedule that conflicts with that of an opioid treatment program, or concerns related to the social stigma associated with methadone [186].

Although the appropriate maintenance dose should be tailored to the individual on the basis of genetics and opioid use history, daily doses of 80–120 mg are common and are more likely to produce the desired opioid-blockade effect. Data indicate a greater reduction in illicit opioid use from a daily dose of 80–100 mg than from a dose of 40–60 mg [183; 186].

A potential issue with methadone relates to its metabolism by the hepatic cytochrome P450 CYP3A4 enzyme and the numerous medications that may adversely interact with its metabolism to result in elevation of plasma methadone level or rapid elimination of the drug. This can lead to dangerous toxicity or lack of effectiveness, respectively [99; 183].

Buprenorphine Therapy

Buprenorphine was the first drug approved for treatment of opioid addiction that can be prescribed in an office-based setting [187]. For use in opioid addiction therapy, buprenorphine is formulated into a product combined with the opioid antagonist naloxone and administered sublingually. When taken as prescribed, the naloxone component remains inert, but if the formulation is crushed and injected, the naloxone is activated to produce withdrawal symptoms. Buprenorphine occupies 85% to 92% of brain mu opioid receptors at 16 mg/day dosing and 94% to 98% at 32 mg/day. Daily doses of 4–16 mg are typically effective for most patients, with 16–24 mg the upper limit of recommended dosing [99; 188; 189]. Prior to January 2023, clinicians had to apply for a federally required Drug Addiction Treatment Act (DATA) Waiver (X-Waiver) in order to prescribe medications, like buprenorphine, for the treatment of opioid use disorder. Section 1262 of the Consolidated Appropriations Act of 2023 (also known as Omnibus bill) removed this requirement and allowed clinicians with schedule III authority on their DEA registration to prescribe buprenorphine if permitted by applicable state law [99; 190].

Several pharmacologic aspects of buprenorphine contribute to its safety and effectiveness as therapy for opioid addiction and make it highly suitable for use in primary care [191]. As a partial mu agonist, a ceiling effect exists for its maximal activity—beyond a certain dose, no additional benefit is experienced. In contrast to increases in the dose of pure opioid agonists such as methadone, a greater margin of safety exists from death by respiratory depression. Buprenorphine possesses a short plasma half-life (about four to six hours) and a long duration of action resulting from its high affinity for and slow dissociation from the mu opioid receptor [187]. This slow dissociation likely contributes to a reduction in the severity of withdrawal symptoms during detoxification, and the longer duration of action allows for the potential of alternate-day dosing [192].

Methadone and Buprenorphine Efficacy

The efficacy literature indicates that higher-dose methadone (>50 mg daily, and 60–100 mg per day in particular) is more effective than lower doses in reducing illicit opioid and possibly cocaine use [193]. Higher-dose methadone is comparable to higher-dose buprenorphine (≥8 mg daily) on measures of treatment retention and reduction of illicit opioid use [193]. Although 30–60 mg per day of methadone may be effective in resolving opioid withdrawal symptoms, some patients require a maintenance dose ≥120 mg per day to eliminate illicit opioid use [193]. Patients requiring high-dose methadone for more severe opioid addiction are unlikely to achieve the same benefit from higher-dose buprenorphine [119]. Methadone has been reported to have higher retention rates, whereas buprenorphine has a lower risk of overdose fatality. These risks should be appropriately weighed by the treating or referring physician [191].

Sustained stabilization on methadone or buprenorphine can greatly enhance the capacity for normal functioning, including holding a job, avoiding crime, and reducing exposure to infectious disease from injection drug use or risky sexual behavior. Stabilized patients are much more likely to benefit from counseling and group therapy, essential components of recovery [185]. Although patients may experience sedation during the induction phase, tolerance to this effect develops over several weeks, after which the ability to work safely or operate a car or machinery is no longer impaired. Cognitive research has found that, during stabilization, the methadone-maintained patient is just as capable as a healthy, non-addicted person in job performance, assuming education and skill is comparable and abstinence from opioids and other drugs of abuse is ongoing [194]. Unfortunately, serious stigma surrounds methadone treatment, experienced most acutely by patients but also by professionals, which may pose a barrier to treatment support [195].

While methadone and buprenorphine can effectively treat pathologic opioid use, they do not appear to significantly reduce non-opioid substance abuse. Both medications are approved for use as part of a broader, comprehensive, recovery-oriented medical and social support plan. Importantly, these medications are compatible with a recovery-oriented treatment approach, which research suggests can be an essential—but not sufficient—element of recovery from opioid addiction [196]. While methadone and buprenorphine can provide the patient with stabilization by suppressing withdrawal symptoms, craving, and dysphoria, many patients also experience mental health problems, deterioration in personal and social relationships, and greatly impaired occupational functioning.

The addition of counseling, social services, monitoring, and peer supports can offer much of what pharmacotherapy cannot provide [186].

The effectiveness of methadone and buprenorphine has only been shown in their use as long-term maintenance, and there is little evidence to support their use as a short-term therapy course. This has been a source of patient and provider frustration. In clinicians, this probably reflects the antiquated perception that withdrawal and craving are the cardinal manifestations of addiction that, if properly treated for a brief period, should lead to full remission. It is now known that no short-term treatment can reverse the typically decades-long opioid-induced genetic expression, neurobiologically based cue-induced craving and withdrawal, or alteration in brain reward, motivation, and memory circuits characterizing long-term opioid addiction. There is increasingly widespread awareness that addiction should be viewed as a chronic disease, with great similarity to other chronic disease, such as diabetes and hypertension, whereby remission is dependent on medical management, lifestyle changes, and significant social supports [186].

Considerations in Addressing Chronic Pain

Although methadone and buprenorphine are highly effective in the treatment of some chronic pain conditions, the protocol by which they are administered to treat opioid use disorder is unlikely to provide sufficient analgesia for patients with chronic pain. With methadone, the 4- to 8-hour duration of analgesic action is significantly shorter than the 24- to 48-hour duration it suppresses opioid withdrawal and craving. The typical once-daily dosing results in a narrow window of analgesia, and contrary to popular belief, it is usually not adequate for analgesia in patients with chronic pain. Additional therapies are required. With patients often describing a six- to eight-hour window of analgesia from their usual morning dose, a single long-acting opioid dose in the afternoon or early evening may be sufficient for pain control for the remainder of the day [197].

With buprenorphine therapy, concurrent opioid analgesic use is complicated by buprenorphine pharmacodynamics. With high mu opioid receptor affinity, buprenorphine displaces or competes with full opioid agonists given concurrently. This can result in several types of adverse outcomes [15]:

- Inadequate analgesia from blocking the effect of concurrent opioids
- Opioid overdose when buprenorphine plasma level declines in the presence of high-dose concurrent opioids
- Acute opioid withdrawal syndrome as the buprenorphine plasma level declines in the presence of inadequate additional opioids
- Acute opioid withdrawal syndrome when buprenorphine is administered to patients receiving long-term opioid analgesic therapy

Buprenorphine has an analgesic duration of 4 to 8 hours and a 24- to 48-hour suppression of opioid withdrawal and craving. As a partial agonist, the analgesic effect has a ceiling after which dose escalation does not lead to improved pain control. Thus, patients receiving buprenorphine for opioid use disorder must discontinue this medication if they require full-agonist opioid analgesics for chronic pain control. Before taking this step, the clinician and patient should weigh the risks and benefits, including the risks of prescription opioid abuse and potential relapse to drug use without buprenorphine, and the potential improvements in pain and function that may come with full-agonist opioid analgesic therapy [20].

Patients in recovery from opioid or other substance use disorders may have specific preferences for types of analgesic medications and may have greater awareness of their risk of relapse if given opioids for their chronic pain. Studies of patients with pain in recovery from substance use disorders have found that while some do relapse when receiving long-term opioid analgesic therapy, untreated pain can itself be a trigger for relapse. A prescription opioid agreement may help provide a sense of control that recovering addicts often fear losing when taking opioid analgesics [20].

CASE STUDY

An unemployed man, 64 years of age, is brought to an emergency department by ambulance, after his wife returned from work to find him lying on the couch, difficult to arouse and incoherent. He has a past history of hypertension, diabetes (non-insulin dependent), mild chronic obstructive pulmonary disease, and chronic back and shoulder pain, for which he has been prescribed hydrocodone/acetaminophen for many years. His wife reports that while he seemed his usual self when she left for work that morning, he had, in recent weeks, been more withdrawn socially, less active, and complained of greater discomfort from the back and shoulder pain. She knows little about his actual medication usage and expresses concern that he may have been taking more than the prescribed amount of "pain medicine."

On evaluation, the patient is somnolent and arouses to stimulation but is non-communicative and unable to follow commands. His blood pressure is normal, he is afebrile, and there are no focal neurologic deficits. Oxygen saturation, serum glucose, and routine laboratory studies (blood counts and metabolic profile) are normal except for mild elevation in blood urea nitrogen (BUN) and creatinine; the urine drug screen is negative except for opioids. Additional history from the family indicates that the patient has been admitted to other hospitals twice in the past three years with a similar presentation and recovered rapidly each time "without anything being found."

Following admission, the patient remains stable-to-improved over the next 12 to 18 hours. By the following day, he is awake and conversant and looks comfortable. On direct questioning, he reports recent symptoms of depression but no suicidal

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ideation. The patient describes an increased preoccupation with his pain syndrome, difficulty sleeping at night, and little physical activity during the day, in part because of physical discomfort. He is vague about his medication regimen and admits to taking "occasional" extra doses of hydrocodone for pain relief.

The family is instructed to bring in all his pill bottles from home, which they do. In addition to the hydrocodone prescribed by his primary care physician, there is a recent refill of a prescription for the medication given to the patient at the time of his last hospital discharge six months earlier.

ASSESSMENT

A full evaluation, including radiographic studies and consultation with psychiatry and physical therapy, is completed. The working diagnosis for the patient's acute illness is toxic encephalopathy caused by the sedative side effects of opioid medication on the CNS. It is explained that the combination of his advancing age and diabetes likely reduced the efficiency of his kidneys in clearing the medication and its metabolites, making him more susceptible to CNS sedation. It is noted that the patient and his wife have little understanding of the rationale, proper use and safeguards, potential side effects, and limited effectiveness of opioid use for chronic pain.

In addition, the patient is diagnosed with poorly controlled chronic pain syndrome secondary to osteoarthritis and degenerative disc disease; exacerbating factors include deconditioning and reactive depression. The use of an opioid analgesic, at least for the near term, is considered appropriate, if dosed properly, monitored closely, and integrated into a comprehensive, multidisciplinary plan that includes treatment of depression and the use of adjunctive, nonpharmacologic modalities of care. In the setting of possible early diabetic nephropathy, the option of utilizing an NSAID, except for very brief periods of breakthrough pain, is not considered to be a safe option.

At discharge, and in consultation with his primary care physician, a written treatment and management plan addressing all aspects of the patient's care is presented to the patient and his wife for discussion and consent. Among the key issues addressed are:

- Goals: Improvement in subjective pain experience; improved function of daily living manifested by regular walking exercise and improved social interaction with family and friends; relief of depression; and in the long-term, anticipated withdrawal of opioid medication and resumption of part-time work and/or volunteer community activity
- Outpatient physical therapy and back exercise program to increase core muscular strength, improve flexibility, reduce pain, and increase exercise tolerance
- Patient and family counseling regarding the safe use, dosage regulation, side effects, and proper disposal of opioid medication
- Joint patient-physician responsibilities as regards to regular follow-up, monitoring of goals and treatment effectiveness, avoidance of "doctor-shopping," and assent to a single provider for prescription medication

FOLLOW-UP

On follow-up six weeks after discharge, the patient is noticeably improved. He reports that he feels stronger and is sleeping better. His affect is brighter, and he is getting out more. He has maintained his physical therapy and exercise routine and is compliant with his medication. Though he still has pain, it is noticeably less and he is coping better. He and his wife are encouraged by his progress, particularly in regard to his improved functional status.

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 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.

APPENDIX: BIAS AND VALIDITY IN PAIN RESEARCH

In addition to training, experience, and clinical judgment, safe and effective treatment of pain is guided by developments in the area of pain medicine research. Clinician awareness of refinements, advances, and breakthroughs in the diagnosis and treatment of pain is most directly acquired from reading the published research. Conducting well-designed clinical research is challenging and complex. Obtaining accurate and relevant information to apply to patient care is often made more difficult by inadvertent bias and lack of reliable validity in the reporting of research findings. Outright data fraud is rare, but false claims and biased interpretation of results (often unintentional) are commonplace in publications of medical research in general and pain research specifically. In the area of pain treatment with opioid analgesics, major stakeholder influence over the reporting of dangers, risks, benefits, and effectiveness is pervasive [2; 97; 198; 199; 200].

Clinicians trying to make the most of their limited time by reading study abstracts may also be misinformed. A random selection of studies with abstracts from six widely read and influential medical journals (*JAMA*, *BMJ*, *Lancet*, *NEJM*, *Annals of Internal Medicine*, and the *Canadian Medical Association Journal*) found that 18% to 68% of abstracts reported information that was inconsistent with or absent from the body of the paper [201].

PUBLICATION BIAS

Publication bias occurs when trials showing statistically significant and positive results are disproportionately published, relative to trials with negative or inconclusive findings. This type of bias is common in published pharmacological research. Pharmaceutical industry research sponsorship is associated with significantly higher rates of pro-industry conclusions, publication constraints, and propensity to ignore the publication of negative findings [202; 203; 204; 205; 206; 207].

REPORTING BIAS

Reporting bias includes a diverse range of bias, misrepresentation, distortion, omission, exaggeration, or dismissal of data reported by the authors of a study or of data from other publications [208]. The effect, if not the intent, of reporting bias is to influence reader perception through a persuasive argument that favors the agenda, paradigm, or interest of the author, agency, or institution, or to diminish or discount a competing or opposing perspective. Reporting bias is just as widespread in pain research as it is in other areas of medicine, often appearing as concluding statements of safety or efficacy that are not supported by the actual evidence.

A medical issue or problem is considered "hot" when it becomes the focal point of publicity and intense investigation. Reports of research findings are less likely to be true in hotter areas of research. Prejudice can dominate a hot medical field to further undermine the validity of research findings. Highly prejudiced stakeholders can also create obstacles and obstruct efforts to publish information with opposing results [209].

Pressures of vested interests can lead to disappointing research outcomes being "spun" to present the findings in a more favorable light by creative use of data, statistics, and linguistics. Examples of linguistic spin include [210]:

- "Treatment X is expected to be a very mportant approach in the management of Disorder Y"
- "Treatment X effect size approached conventional statistical significance."

The use of "spin"—claiming treatment benefit without any supporting evidence from the data—is common, and safety claims with spin without supporting data also occur [211; 212; 213].

BIAS IN CLINICAL PRACTICE GUIDELINES

Concerns have sometimes been raised regarding bias in the development of clinical practice guidelines, involving the reviewed research, misrepresentation of the data, or failure to assess the quality of the evidence supporting the recommendations. Inadequate or weak evidence may lead to conclusions based on value judgments, organizational preferences, or opinion. Guidance is frequently misinterpreted as mandate, when individualized treatment is the best practice [214]. Clinical practice guideline authority and influence usually comes from the sponsoring organization and status of the publishing journal. Once issued, the organization may become the promoter and defender of the guidelines, and panel members the stakeholders in the acceptance of their recommendations [115; 215].

Bias can also negatively affect the validity of systematic reviews and meta-analyses that can form the basis of clinical practice guidelines. For example, several practice guidelines on long-term opioid therapy for chronic pain were published between 2008 and 2011. Although each guideline was based on analysis of essentially the same body of published research, the guideline conclusions differed markedly. The educated reader may look deeper for possible explanations for these discrepancies, including bias. Areas to explore would include the source of funding or sponsorship for development and financial and other material ties of the authors to industry, organization, or agency (e.g., slanted reporting of findings, conclusions consistent with industry of agency interests or agenda); the quality of evidence used to support a recommendation (by either endorsing or discouraging use of a drug, dose level, or therapy duration) and, in particular, weak evidence used inappropriately as definitive proof; whether the authors solely used published studies; and whether the studies used were industry funded [216].

FALLACIES OF ARGUMENT

Fallacies of evidence or argument are used in pain medicine research to support or defend a false conclusion (***Table 12***). Many are intended to convince the reader of a cause-effect relationship when the actual evidence is weak or absent. Considerable evidence is required to establish a true cause-effect relationship, and the evidence purported to show causation may actually reflect association instead. It is important to maintain a degree of critical thinking to avoid being persuaded into accepting a falsehood or rejecting a truth.

Cum Hoc, Ergo Propter Hoc Fallacy

A prototypical example of this type of fallacy comes from the 2011 CDC reporting of the same data in three publications related to a stated epidemic in opioid analgesic deaths and addiction and their direct relation to increasing opioid prescribing as reflected by sales data. Evidence to support this argument came from simultaneously increased trends in opioid analgesic sales, opioid analgesic overdose deaths, and

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ARGUMENTS USED TO SUPPORT ERRONEOUS CONCLUSIONS IN BIASED RESEARCH REPORTING		
Form of Argument	**Definition**	**Explanation or Example**
False conclusions of causation based on correlation		
Non causa pro causa (no cause for cause)	One or more events suggested as causing another event	Even when data show a statistically significant correlation, assumption of cause and effect is erroneous.
Cum hoc, ergo propter hoc (with this, therefore because of this)	Causation based on an association between two or more event trends or outcomes that occur together in time	1) The correlation may be significant, but correlation is not causation, and more research is needed to rule out other explanations for the association. 2) The direction of causation may be the reverse of the false conclusion.
Post hoc, ergo propter hoc (after this, therefore because of this)	Conclusion of causality based solely on the sequence of events	This is common in observational and open-label studies, because factors that actually influence outcome are not controlled for.
Regression fallacy	Pain severity declines over time to a lower average level during the natural course.	This "regression to the mean" can falsely be attributed to treatment effect.
Texas sharpshooter fallacy	Certain variables showing a close association are selected from a vast array of data, and a cause-effect relationship is concluded.	Common in data-mining studies and erroneous due to: 1) The data cluster may be the result of chance. 2) Even if not random, the cause may differ from what is stated by the researchers.
False arguments used in support of a conclusion		
Argumentum ad ignoratum (appeal to ignorance)	Missing evidence is itself evidence for lack of an effect.	Often seen in pain medicine, as when the lack of long-term controlled studies on opioid safety and efficacy in chronic pain is stated as evidence against long-term opioid use in chronic pain
Argumentum ad verecundiam (appeal to authority)	The high-status source of a publication is used to affirm the results.	In an argument with weak factual support, this is used to mislead the reader into not questioning the accuracy, reliability, or validity of the data the argument is based on.
Argumentum ad populum (appeal to the people or popularity)	The widespread use and acceptance of a practice prove its validity.	Argues that a popular treatment (e.g., homeopathic pain remedies) would not be so widely used if it did not work. Avoids the need to show credible evidence.
Illusory correlation	An expected relationship between data, observations, or events is found when a true causal relationship is absent.	This fallacy has been used when infrequent patient outcomes stand out and are generalized to represent all patient outcomes.
Reductionism	A large, complex phenomenon is oversimplified by reducing it to a smaller, simpler component.	Can occur when data from a small, highly select group of patients with pain, or even data of individual patients by anecdote, is used to characterize an entire population of patients.
The "no true Scotsman" fallacy	Used as an *ad hoc* rescue of a reductionist argument that comes under criticism	Reflected by statements such as "no true patient in pain would abuse their medication"
False dichotomy	Forces simple answers to complex questions with an argument in which only two choices are offered	Epidemiologic studies may record the rate of opioid abuse by the number persons who either did or did not ingest a non-prescribed opioid analgesic in the past year. This neglects any detailed analysis, such as motivation by untreated pain, inadequately treated pain, or desire to get high.
Myths of beneficence	Programs or policies are argued as beneficial to patients or the public and thus should be accepted.	This appeal to altruism and the presumption of good intentions may be used to deter examination of possibly deficient or biased reasoning or harmful unintended consequences.

Source: [217; 218] *Table 12*

addiction treatment admissions for opioid analgesics [212; 213; 219]. Many professionals found this persuasive evidence of a cause-effect relationship, and this conclusion was also reported by the news media and widely referenced in academic papers.

With causation inferred from correlational data, the fallacy in this reporting was that few alternate explanations for the correlations were presented. One credible explanation would have been exaggeration in the true rates of unintended overdose fatalities directly caused by opioid analgesics, a fact conceded by the CDC. Omitted entirely was discussion of the escalating population of patients with chronic pain. Sicker patients may also have been increasingly prescribed multiple medications with overdose potential for their disorders, including opioids.

Another reason that causal inference from correlational data is erroneous is that when causation is based on simultaneously occurring events, it is not possible to determine which event came first. The true direction of causation may actually be the reverse of that reported by researchers. For instance, studies finding a significant correlation between fibromyalgia and obesity in women concluded these female patients developed fibromyalgia because they were overweight. The order of events, such as whether obesity or fibromyalgia came first, was never examined, and it is just as likely the pain and disability associated with fibromyalgia promoted activity avoidance and weight gain or that medications used to treat fibromyalgia promoted weight gain or that medications used to treat fibromyalgia promoted weight gain.

False conclusions of a cause-effect relationship may also occur when data used in support of a conclusion come from small but statistically significant outcomes in a measure of effect, when broader examination of the data suggests otherwise. One example is the conclusion of a cause-effect relationship between higher methadone dose and frequency of the serious adverse cardiac event of QTc interval prolongation. The basis of this conclusion of causality was the finding of a modest yet statistically significant correlation between higher dose and adverse event [220; 221]. However, the conclusion is false because correlation does not equate with causality, and a closer look at the actual data revealed that increased QT interval occurred only in the subgroup who were abusing cocaine, a drug with well-known cardiotoxic effects.

Post Hoc Fallacy

An example of *post hoc* fallacy in reasoning comes from a prospective, observational, open-label study in which single-dose intrathecal midazolam was used in patients with failed back surgery syndrome. The patients showed significant pain reduction and few side effects, and the researchers concluded that single-dose intrathecal midazolam was an effective supplement to standard analgesic therapy [222].

This study was criticized for using a *post hoc, ergo propter hoc* argument as the basis for causation in a commentary published in the same journal issue [223]. The commentary noted that just because patients improved after midazolam treatment did not mean they improved because of midazolam treatment. From an evidence-based perspective, the study evidence would also be regarded as low quality because it lacked a control group and the open-label design did not control for placebo response.

Differences in Definitions

Differences in definitions also represent a serious confounding factor. Opioid "misuse" may describe overuse or underuse for medical purposes, nonmedical use, or diversion, and may be a one-time occurrence or more frequent. There is little clarity or consistency across studies in how this variable is defined and measured. Consequently, the prevalence rate of opioid misuse can be expressed as a large or small probability depending on the study biases. This same phenomenon occurs with many other variables studied in pain management and can be very misleading to consumers of research.

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COURSE TEST - #91413 PRESCRIPTION OPIOIDS: RISK MANAGEMENT AND STRATEGIES FOR SAFE USE

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 15 Hour activity must be completed by August 31, 2026.

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

2. The fifth revised edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5-TR) categorizes prescription opioid addiction as
- A) *tolerance.*
- B) *substance abuse.*
- C) *substance dependence.*
- D) *substance use disorder.*

3. Which of the following is NOT a characteristic of substance addiction according to the American Society of Addiction Medicine?
- A) *Inability to consistently abstain*
- B) *Impairment in behavioral control*
- C) *A functional emotional response*
- D) *Diminished recognition of significant problems with one's behaviors and interpersonal relationships*

4. Which of the following is TRUE regarding aberrant drug use/seeking behaviors?
- A) *They occur at very low rates.*
- B) *They almost always reflect an emerging opioid use problem.*
- C) *They can always be predicted with careful pre-opioid therapy assessment.*
- D) *Even when strongly suggestive of opioid use disorder, they can be driven by relief seeking for physical (pain) or emotional distress.*

5. 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*

6. Which of the following has NOT contributed to the historic, widespread pattern of pain undertreatment in the United States?
- A) *Absence of effective analgesic medications*
- B) *Fear of patient addiction if opioids were prescribed*
- C) *Concerns over regulatory scrutiny and sanction if opioids were prescribed*
- D) *Dismissal of pain as an endurable symptom of a primary illness or condition*

7. Which of the following did NOT contribute to broad expansion and indications for opioid prescribing for pain in the 1990s to early 2000s?
- A) *DEA cooperation*
- B) *FSMB reassurance*
- C) *Congressional legislature*
- D) *Pharmaceutical industry influence*

8. Which of the following opioids showed increased retail purchases from 2019 to 2021?
- A) *Fentanyl*
- B) *Methadone*
- C) *Meperidine*
- D) *Hydromorphone*

9. Which of the following is FALSE regarding extended-release opioids before the 1990s?
- A) *Most of the agents required IV or IM administration.*
- B) *Their outpatient use was mainly limited to cancer patients.*
- C) *Their use was mostly limited to operating room and inpatient settings.*
- D) *They were widely available to outpatients, but under very strict controls.*

Test questions continue on next page ➜

10. Which of the following has NOT contributed to the increasing prevalence of chronic pain?
- *A) The aging population*
- *B) Advances in lifesaving trauma interventions*
- *C) Rising rates of obesity and obesity-related pain conditions*
- *D) Poor public awareness of pain as a condition warranting medical attention*

11. Americans consume what percentage of worldwide hydrocodone consumption?
- *A) 35%*
- *B) 55%*
- *C) 80%*
- *D) 99%*

12. As of April 2020, how many states have passed laws that address opioid analgesic prescribing?
- *A) 5*
- *B) 20*
- *C) 40*
- *D) All 50 and the District of Columbia*

13. As of 2023, more than 90% of opioid prescriptions have been for
- *A) ER/LA opioids.*
- *B) short-acting opioids.*
- *C) immediate-release opioids.*
- *D) Both B and C*

14. Which of the following factors influences the decision to prescribe an opioid analgesic?
- *A) Patient preference*
- *B) Clinician knowledge and judgment*
- *C) Aggressive pharmaceutical marketing*
- *D) All of the above*

15. Which of the following is NOT true of trends in opioid analgesic misuse/abuse-related emergency department (ED) visits?
- *A) The ED admit rate increased 153% from 2004 to 2011.*
- *B) Morphine-related ED admits increased 144% from 2004 to 2011.*
- *C) The overall rate of ED admits has been unchanged from 2009 to 2011.*
- *D) Hydrocodone was the most frequent opioid involved in ED admits in 2011.*

16. In 2021, approximately how many persons engaged in nonmedical use of prescription opioids?
- *A) 500,000*
- *B) 2 million*
- *C) 9.2 million*
- *D) 25 million*

17. In 2021, the most frequent initial illicit drug experience was with
- *A) cannabis.*
- *B) tranquilizers.*
- *C) prescription opioids.*
- *D) prescription stimulants.*

18. In 2021, how many persons in the United States had misused both heroin and prescription opioid analgesics?
- *A) 574,000*
- *B) 1.2 million*
- *C) 8.7 million*
- *D) 12 million*

19. In 2021, the past-year treatment admissions for opioid use disorders
- *A) decreased.*
- *B) increased.*
- *C) plateaued and then declined.*
- *D) declined and then plateaued.*

20. Of those who misuse or abuse prescription opioids, what percentage report having obtained their most recently used drugs from a friend or relative for free?
- *A) 4.3%*
- *B) 13.7%*
- *C) 21.2%*
- *D) 33.9%*

21. Which of the following is NOT a known risk factor for fatal opioid toxicity?
- *A) Body mass index less than 30*
- *B) Prescriber error due to knowledge deficits*
- *C) Patient non-adherence to medication regimen*
- *D) Co-administration of other CNS-depressant drugs, including alcohol or benzodiazepines*

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22. Which of the following statements regarding the escalation in methadone prescribing and fatal toxicity between 1997 and 2007 is FALSE?
- A) *Plasma half-life vastly exceeds the duration of analgesia.*
- B) *The majority of fatalities occur more than two weeks after initiation of treatment.*
- C) *Until 2006, the recommended analgesic dosing interval was every three to four hours.*
- D) *All of the above*

23. As reflected by trends in arrestee data, the prescription opioid abuse epidemic is
- A) *escalating.*
- B) *incubating.*
- C) *increasing at a slower rate.*
- D) *past peak and trending downward.*

24. Publication of the 2013 FSMB model policy was prompted by findings of additional contributing factors to pain undertreatment and inappropriate opioid prescribing, which include all of the following, EXCEPT:
- A) *Conflicting clinical guidelines*
- B) *Knowledge gaps in medical standards*
- C) *Undue emphasis on pain as a distinct pathologic entity*
- D) *Prescriber concerns over regulatory or law enforcement attention from legitimate opioid prescribing*

25. Which of the following is NOT a characteristic of appropriate opioid prescribing?
- A) *Appropriately documented*
- B) *Demonstrable patient benefit*
- C) *Failure to use risk assessment tools*
- D) *Based on sound clinical judgment and current best clinical practices*

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

27. 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*

28. Which of the following is one of the ten essential steps of opioid prescribing for chronic pain that can help mitigate any potential problems?
- A) *Patient preference*
- B) *Trials of opioid monotherapy only*
- C) *Diagnosis with an appropriate differential*
- D) *A single assessment of substance abuse risk*

29. 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*

30. 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.*

31. When using urine drug testing to monitor adherence and compliance, it is important to
- A) *understand the limitations.*
- B) *always use manufacturer recommended testing frequency.*
- C) *aggressively confront patients with results suggesting non-use of a prescribed opioid.*
- D) *use immunoassay point-of-care results as the basis of important clinical decisions.*

32. The U.S. Food and Drug Administration recommends that unused OxyContin tablets be disposed of by
- A) *burning.*
- B) *flushing down the toilet.*
- C) *throwing in the garbage in a sealed container.*
- D) *sharing with a friend or relative with chronic pain.*

Test questions continue on next page ➞

33. An opioid should be safely discontinued with
- A) *inadequate analgesia.*
- B) *resolution of the pain syndrome.*
- C) *significant aberrant medication use.*
- D) *All of the above*

34. Which of the following is an advantage of abuse-deterrent opioid formulations utilizing aversive components?
- A) *Very little risk for adverse events*
- B) *Several approved FDA formulations exist*
- C) *May limit abuse by chewing or crushing the product*
- D) *Prevents accidental crushing or chewing in compliant patients*

35. The introduction of abuse-deterrent OxyContin has resulted in
- A) *no effect in the rates of OxyContin abuse/addiction.*
- B) *decreased rates of OxyContin abuse/addiction and increased rates of heroin abuse/addiction.*
- C) *a uniform decrease in abuse/addiction rates of prescription and street opioids.*
- D) *decreased rates of OxyContin abuse/addiction and no change in other opioids.*

36. The ARCOS system that monitors the flow of controlled substances through the distribution chain is run by the
- A) *DEA.*
- B) *FDA.*
- C) *CDC.*
- D) *SAMHSA.*

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

38. Patients who require ultra-high-dose opioids to control chronic pain should be restricted from the use of
- A) *sedatives.*
- B) *benzodiazepines.*
- C) *muscle relaxants.*
- D) *All of the above*

39. Nonpharmacologic approaches shown to be effective for the treatment of substance use disorder in patients with chronic pain include all of the following, EXCEPT:
- A) *Mindfulness meditation*
- B) *12-step program involvement*
- C) *Cognitive-behavioral therapy*
- D) *Psychodynamic psychotherapy*

40. Which of the following is NOT an advantage of buprenorphine over methadone treatment of opioid use disorder in patients with chronic pain?
- A) *Less stigma*
- B) *Higher retention rates*
- C) *Longer duration of action*
- D) *Greater safety margin in overdose*

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