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Cultural Competence: An Overview

This course meets the new California requirement for cultural competency and humility education.

Audience
This course is designed for all members of the interprofessional healthcare team.

Course Objective
The purpose of this course is to provide members of the interprofessional healthcare team with the knowledge, skills, and strategies necessary to provide culturally competent and responsive care to all patients.

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

1. Define cultural competence, implicit bias, and related terminology.
2. Outline social determinants of health and barriers to providing care.
3. Discuss best practices for providing culturally competent care to various patient populations.
4. Discuss key aspects of creating a welcoming and safe environment, including avoidance of discriminatory language and behaviors.

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Alice Yick Flanagan, PhD, MSW, received her Master's in Social Work from Columbia University, School of Social Work. She has clinical experience in mental health in correctional settings, psychiatric hospitals, and community health centers. In 1997, she received her PhD from UCLA, School of Public Policy and Social Research. Dr. Yick Flanagan completed a year-long post-doctoral fellowship at Hunter College, School of Social Work in 1999. In that year she taught the course Research Methods and Violence Against Women to Masters degree students, as well as conducting qualitative research studies on death and dying in Chinese American families. (A complete biography can be found at NetCE.com.)

Faculty Disclosure
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INTRODUCTION

Culturally competent care has been defined as "care that takes into account issues related to diversity, marginalization, and vulnerability due to culture, race, gender, and sexual orientation" [1]. A culturally competent person is someone who is aware of how being different from the norm can be marginalizing and how this marginalization may affect seeking or receiving health care [1]. To be effective cross-culturally with any diverse group, healthcare professionals must have awareness, sensitivity, and knowledge about the culture involved, enhanced by the use of cross-cultural communication skills [2; 3].

Healthcare professionals are accustomed to working to promote the healthy physical and psychosocial development and well-being of individuals within the context of the greater community. For years, these same professionals have been identifying at-risk populations and developing programs or making referrals to resources to promote the health and safety of at-risk groups. But, because of general assumptions, persistent stereotypes, and implicit and explicit biases, culture-related healthcare disparities persist [2]. In the increasingly diverse landscape of the United States, assessing and addressing culture-related barriers to care are a necessary part of health care. This includes seeking to improve one's cultural competence and identifying blind spots and biases.

DEFINITIONS

CULTURAL COMPETENCE

In healthcare, cultural competence is broadly defined as practitioners' knowledge of and ability to apply cultural information and appreciation of a different group's cultural and belief systems to their work [4]. It is a dynamic process, meaning that there is no endpoint to the journey to becoming culturally aware, sensitive, and competent. Some have argued that cultural curiosity is a vital aspect of this approach.

CULTURAL HUMILITY

Cultural humility refers to an attitude of humbleness, acknowledging one's limitations in the cultural knowledge of groups. Practitioners who apply cultural humility readily concede that they are not experts in others' cultures and that there are aspects of culture and social experiences that they do not know. From this perspective, patients are considered teachers of the cultural norms, beliefs, and value systems of their group, while practitioners are the learners [5]. Cultural humility is a lifelong process involving reflexivity, self-evaluation, and self-critique [6].

DISCRIMINATION

Discrimination has traditionally been viewed as the outcome of prejudice [7]. It encompasses overt or hidden actions, behaviors, or practices of members in a dominant group against members of a subordinate group [8]. Discrimination has also been further categorized as lifetime, which consists of major discreet discriminatory events, or everyday, which is subtle, continual, and part of day-to-day life and can have a cumulate effect on individuals [9].

DIVERSITY

Diversity "encompasses differences in and among societal groups based on race, ethnicity, gender, age, physical/mental abilities, religion, sexual orientation, and other distinguishing characteristics" [10]. Diversity is often incorrectly conceptualized into singular dimensions as opposed to multiple and intersecting diversity factors [11].

INTERSECTIONALITY

Intersectionality is a term to describe the multiple facets of identity, including race, gender, sexual orientation, religion, sex, and age. These facets are not mutually exclusive, and the meanings that are ascribed to these identities are inter-related and interact to create a whole [12]. This term also encompasses the ways that different types and systems of oppression intersect and affect individuals.

PREJUDICE

Prejudice is a generally negative feeling, attitude, or stereotype against members of a group [13]. It is important not to equate prejudice and racism, although the two concepts are related. All humans have prejudices, but not all individuals are racist. The popular definition is that "prejudice plus power equals racism" [13]. Prejudice stems from the process of ascribing every member of a group with the same attributes [14].

RACISM

Racism is the "systematic subordination of members of targeted racial groups who have relatively little social power...by members of the agent racial group who have relatively more social power" [15]. Racism is perpetuated and reinforced by social values, norms, and institutions.

There is some controversy regarding whether unconscious (implicit) racism exists. Experts assert that images embedded in our unconscious are the result of socialization and personal observations, and negative attributes may be unconsciously applied to racial minority groups [16]. These implicit attributes affect individuals' thoughts and behaviors without a conscious awareness.

Structural racism refers to the laws, policies, and institutional norms and ideologies that systematically reinforce inequities, resulting in differential access to services such as health care, education, employment, and housing for racial and ethnic minorities [17; 18].

BIAS: IMPLICIT AND EXPLICIT

In a sociocultural context, biases are generally defined as negative evaluations of a particular social group relative to another group. Explicit biases are conscious, whereby an individual is fully aware of his/her attitudes and there may be intentional behaviors related to these attitudes [19]. For example, an individual may openly endorse a belief that women are weak and men are strong. This bias is fully conscious and is made explicitly known. The individual's ideas may then be reflected in his/her work as a manager.

FitzGerald and Hurst assert that there are cases in which implicit cognitive processes are involved in biases and conscious availability, controllability, and mental resources are not [20]. The term "implicit bias" refers to the unconscious attitudes and evaluations held by individuals. These individuals do not necessarily endorse the bias, but the embedded beliefs/attitudes can negatively affect their behaviors [21; 22; 23; 24]. Some have asserted that the cognitive processes that dictate implicit and explicit biases are separate and independent [24].

Implicit biases can start as early as 3 years of age. As children age, they may begin to become more egalitarian in what they explicitly endorse, but their implicit biases may not necessarily change in accordance to these outward expressions [25]. Because implicit biases occur on the subconscious or unconscious level, particular social attributes (e.g., skin color) can quietly and insidiously affect perceptions and behaviors [26]. According to Georgetown University's National Center on Cultural Competency, social characteristics that can trigger implicit biases include [27]:

- Age
- Disability
- Education
- English language proficiency and fluency
- Ethnicity
- Health status
- Disease/diagnosis (e.g., human immunodeficiency virus [HIV])
- Insurance
- Obesity
- Race
- Socioeconomic status
- Sexual orientation, gender identity, or gender expression
- Skin tone
- Substance use

An alternative way of conceptualizing implicit bias is that an unconscious evaluation is only negative if it has further adverse consequences on a group that is already disadvantaged or produces inequities [20; 28]. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages [28].

When the concept of implicit bias was introduced in the 1990s, it was thought that implicit biases could be directly linked to behavior. Despite the decades of empirical research, many questions, controversies, and debates remain about the dynamics and pathways of implicit biases [21].

Specific conditions or environmental risk factors have been associated with an increased risk for certain implicit biases, including [130; 131]:

- Stressful emotional states (e.g., anger, frustration)
- Uncertainty
- Low-effort cognitive processing
- Time pressure
- Lack of feedback
- Feeling behind with work
- Lack of guidance
- Long hours
- Overcrowding
- High-crises environments
- Mentally taxing tasks
- Juggling competing tasks

ROLE OF INTERPROFESSIONAL COLLABORATION AND PRACTICE

The study of implicit bias is appropriately interdisciplinary, representing social psychology, medicine, health psychology, neuroscience, counseling, mental health, gerontology, gender/sexuality studies, religious studies, and disability studies [28]. Therefore, implicit bias empirical research and curricula training development lends itself well to interprofessional collaboration and practice (ICP).

The main characteristics of ICP allow for implicit and explicit biases to be addressed by the interprofessional team. One of the core features of ICP is sharing—professionals from different disciplines share their philosophies, values, perspectives, data, and strategies for planning of interventions [29]. ICP also involves the sharing of roles, responsibilities, decision making, and power [30]. Everyone on the team employs their expertise, knowledge, and skills, working collectively on a shared, patient-centered goal or outcome [30; 31].

Another feature of ICP is interdependency. Instead of working in an autonomous manner, each team member's contributions are valued and maximized, which ultimately leads to synergy [29]. At the heart of this are two other key features: mutual trust/respect and communication [31]. In order to share responsibilities, the differing roles and expertise are respected.

Experts have recommended that a structural or critical theoretical perspective be integrated into core competencies in healthcare education to teach students about implicit bias, racism, and health disparities [32]. This includes [32]:

- Values/ethics: The ethical duty for health professionals to partner and collaborate to advocate for the elimination of policies that promote the perpetuation of implicit bias, racism, and health disparities among marginalized populations.
- Roles/responsibilities: One of the primary roles and responsibilities of health professionals is to analyze how institutional and organizational factors promote racism and implicit bias and how these factors contribute to health disparities. This analysis should extend to include one's own position in this structure.
- Interprofessional communication: Ongoing discussions of implicit bias, perspective taking, and counter-stereotypical dialogues should be woven into day-to-day practice with colleagues from diverse disciplines.
- Teams/teamwork: Health professionals should develop meaningful contacts with marginalized communities in order to better understand whom they are serving.

Adopting approaches from the fields of education, gender studies, sociology, psychology, and race/ethnic studies can help build curricula that represent a variety of disciplines [33]. Students can learn about and discuss implicit bias and its impact, not simply from a health outcomes perspective but holistically. Skills in problem-solving, communication, leadership, and teamwork should be included [33].

SOCIAL DETERMINANTS OF HEALTH

Social determinants of health are the conditions in the environments where people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks. These circumstances are shaped by the distribution of money, power, and resources at global, national, and local levels. Healthy People 2030 groups social determinants of health into five categories [34]:

- Economic stability
- Education access and quality
- Health care access and quality
- Social and community context
- Neighborhood and built environment

These factors have a major impact on people's health, well-being, and quality of life. Examples of social determinants of health include [34]:

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

Social determinants of health also contribute to wide health disparities and inequities. For example, people who lack access to grocery stores with healthy foods are less likely to have good nutrition, which raises the risk of heart disease, diabetes, and obesity and lowers life expectancy compared with those who have easier access to healthy foods [34].

Promoting healthy choices will not eliminate these and other health disparities. Instead, public health organizations and their partners must take action to improve the conditions in people's environments. Healthcare providers play a role by identifying factors affecting the health of their patients, providing resources (when appropriate), and advocating for healthy environments.

BARRIERS TO PROVIDING CARE

Culturally diverse patients experience a variety of barriers when seeking health and mental health care, including:

- Immigration status
- Lower socioeconomic status
- Language barriers
- Cultural differences
- Lack of or poor health insurance coverage
- Fear of or experiences with provider discrimination
- Mistrust of healthcare systems

Such obstacles can interfere with or prevent access to treatment and services, compromise appropriate referrals, affect compliance with recommendations, and result in poor outcomes. Culturally competent providers build and maintain rich referral resources to meet patients' assorted needs.

Encountering discrimination when seeking health or mental health services is a barrier to optimal care and contributor to poorer outcomes in under-represented groups. Some providers will not treat patients because of moral objections, which can affect all groups, but particularly those who are gender and/or sexual minorities, religious minorities, and/or immigrants. In fact, in 2016, Mississippi and Tennessee passed laws allowing health providers to refuse to provide services if doing so would violate their religious beliefs [35]. However, it is important to remember that providers are obligated to act within their profession's code of ethics and to ensure patients receive the best possible care.

BEST PRACTICES FOR CULTURALLY RESPONSIVE CARE

The U.S. Department of Health and Human Services has outlined steps important to incorporate in evaluation and treatment planning processes to ensure culturally competent clinical and programmatic decisions and skills [36].

The first step is to engage patients. In nonemergent situations, it is important to establish rapport before asking a series of assessment questions or delving deeply into history taking. Providers should use simple gestures as culturally appropriate (e.g., handshakes, facial expressions, greetings) to help establish a first impression. The intent is that all patients feel understood and seen following each interaction. Culturally responsive interview behaviors and paperwork should be used at all times [36].

When engaging in any patient teaching, remember that individuals may be new to the specific language or jargon and expectations of the diagnosis and care process. Patients should be encouraged to collaborate in every step of their care. This consists of seeking the patient's input and interpretation and establishing ways they can seek clarification. Patient feedback can then be used to help identify cultural issues and specific needs. If appropriate, collaboration should extend to include family and community members.

Assessment should incorporate culturally relevant themes in order to more fully understand patients and identify their cultural strengths and challenges. Themes include [36]:

- Immigration history
- Cultural identity and acculturation
- Membership in a subculture
- Beliefs about health, healing, and help-seeking
- Trauma and loss

In some cases, it may be appropriate and beneficial to obtain culturally relevant collateral information, with the patient's permission, from sources other than the patient (e.g., family or community members) to better understand beliefs and practices that shape the patient's cultural identity and understanding of the world.

Practitioners should work to identify screening and assessment tools that have been translated into or adapted for other languages and have been validated for their particular population group(s). An instrument's cultural applicability to the population being served should be assessed, keeping in mind that research is limited on the cross-cultural applicability of specific test items or questions, diagnostic criteria, and concepts in evaluative and diagnostic processes [36].

Typically, culturally responsive care establishes holistic treatment goals that include objectives to improve physical health and spiritual strength; utilizes strengths-based strategies that fortify cultural heritage, identity, and resiliency; and recognizes that treatment planning is a dynamic process that evolves along with an understanding of patient history and treatment needs.

In addition to these general approaches, specific considerations may be appropriate for specific populations. While discussion of every possible patient subgroup is outside of the scope of this course, some of the most common factors are outlined in the following sections [36].

RACIAL BACKGROUNDS

Race and color impact the ways in which individuals interact with their environments and are perceived and treated by others. Race is defined as groups of humans divided on the basis of inherited physical and behavioral differences. As part of the cultural competence process and as a reflection of cultural humility, practitioners should strive to learn as much as possible about the specific racial/ethnic populations they serve [37]. However, considerable diversity exists within any specific culture, race, or ethnicity [37]. Cultural beliefs, traditions, and practices change over time, both through generations and within an individual's lifetime. It is also possible for the differences between two members of the same racial/ethnic group to be greater than the differences between two people from different racial/ethnic groups. Within-group variations in how persons interact with their environments and specific social contexts are also often present.

As with all patients, it is vital to actively listen and critically evaluate patient relationships. All practitioners should seek to educate themselves regarding the experiences of patients who are members of a community that differs from their own. Resources and opportunities to collaborate may be available from community organizations and leaders.

Finally, preferred language and immigration/migration status should be considered. Interpreters should be used when appropriate, with adherence to best practices for the use of interpretation services. Stressing confidentiality and privacy is particularly important for undocumented workers or recent immigrants, who may be fearful of deportation.

Black Patients

"Black" or "African American" is a classification that serves as a descriptor; it has sociopolitical and self-identification ramifications. The U.S. Census Bureau defines African Americans or Black Americans as persons "having origins in any of the Black racial groups of Africa" [38].

According to the U.S. Census, African Americans number 46.9 million as of 2020 [39]. By 2060, it is projected they will comprise 17.9% of the U.S. population [40]. This group tends to be young; 30% of the African American population in the United States is younger than 18 years of age. In 2019, the median age for this group was 35 years [41]. In terms of educational attainment, 89.4% of African Americans 25 years of age or older had a high school diploma or completed college in 2020 [39]. Texas has the largest African American population, at 3.9 million [41].

Historical adversity and institutional racism contribute to health disparities in this group. For the Black population, patient assessment and treatment planning should be framed in a context that recognizes the totality of life experiences faced by patients. In many cases, particularly in the provision of mental health care, equality is sought in the provider-patient relationship, with less distance and more disclosing. Practitioners should assess whether their practices connect with core values of Black culture, such as family, kinship, community, and spirituality. Generalized or Eurocentric treatment approaches may not easily align with these components of the Black community [42]. Providers should also consider the impact of racial discrimination on health and mental health among Black patients. Reports indicate that expressions of emotion by Black patients tend to be negatively misunderstood or dismissed; this reflects implicit or explicit biases.

Asian Patients

As of 2019, 22.9 million Americans identified as Asian [43]. Between 2000 and 2019, Asians experienced the greatest growth compared with any other racial group at 81% [44; 45]. The Chinese group represents the largest Asian subgroup in the United States, and it is projected that this population will grow to 35.7 million between 2015 and 2040 [46; 47]. In 2019, Chinese Americans (excluding Taiwanese Americans) numbered at 5.2 million [43]. They also have the highest educational attainment; 54.6% of Asians 25 years of age or older had a bachelor's degree or higher in 2019 [43].

"Asian" is a single term widely used to describe individuals who have kinship and identity ties to Asia, including the Far East, Southeast Asia, and the Indian subcontinent [48]. This encompasses countries such as China, Japan, Korea, Vietnam, Cambodia, Thailand, India, Pakistan, and the Philippines. Pacific Islander is often combined with Asian American in census data. The Pacific Islands include Hawaii, Guam, Samoa, Fiji, and many others [48]. There are more than 25 Asian/Pacific Islander groups, each with a different migration history and widely varying sociopolitical environments in their homelands [49].

Asian American groups have differing levels of acculturation, lengths of residency in the United States, languages, English-speaking proficiency, education attainment, socioeconomic statuses, and religions. For example, there are approximately 32 different languages spoken among Asian Americans, and within each Asian subgroup (e.g., Chinese), multiple dialects may be present [49; 50]. In 2019, California had the largest Asian American population, totaling 5.9 million [44].

Recommended best practices when caring for Asian American patients include:

- Create an advisory committee using representatives from the community.
- Incorporate cultural knowledge and maintain flexible attitudes.
- Provide services in the patients' primary language.
- Develop culturally specific questionnaires for intake to capture information that may be missed by standard questionnaires.
- Emphasize traditional values and incorporate traditional practices (e.g., acupuncture) into treatment plans, when appropriate and desired.
- Explore patient coping mechanisms that draw upon cultural strengths.

Latino/a/x or Hispanic Patients

In 2020, the Hispanic population in the United States numbered 60.6 million [51]. The majority of the Hispanic population in the United States (63.3%) identify themselves as being of Mexican descent [53]. Approximately 27% of the U.S. Hispanic population identify as Puerto Rican, Cuban, Salvadoran, Dominican, Guatemalan, Colombian, Honduran, Ecuadorian, or Peruvian [54].

In 2020, the Hispanic population comprised 18.7% of the U.S. population [51]. As such, they are the largest ethnic minority group in the United States. By 2060, Hispanics are expected to represent 31% of the U.S. population [55]. They are also a young group, with a median age of 29.8 years [51]. In 2019, the three states with the largest Hispanic population growth were Texas (2 million), California (1.5 million), and Florida (1.4 million); these three states have the largest Hispanic populations overall [52].

When involved in the care of Latinx/Hispanic individuals, practitioners should strive to employ *personalismo* (warm, genuine communication) and recognize the importance of *familismo* (the centrality of the family). More flexible scheduling strategies may be more successful with this group, if possible, and some patients may benefit from culturally specific treatment and ethnic and gender matching with providers. Aspects of Latino culture can be assets in treatment: strength, perseverance, flexibility, and an ability to survive.

Native American Patients

The Native American population is extremely diverse. According to the U.S. Census, the terms "Native American," "American Indian," or "Alaskan Native" refer to individuals who identify themselves with tribal attachment to indigenous groups of North and South America [56]. In the United States, there are 574 federally recognized tribal governments and 324 federally recognized reservations [57].

In 2020, it was reported that there were 7.1 million Native Americans in the United States, which is approximately 2% of the U.S. population [57]. By 2060, this number is projected to increase to 10.1 million, or 2.5% of the total population [57].

In general, this group is young, with a median age of 31 years, compared with the general median age of 37.9 years [58]. As of 2018, the states with the greatest number of residents identifying as Native American are Alaska, Oklahoma, New Mexico, South Dakota, and Montana [59]. In 2016, this group had the highest poverty rate (26.2%) of any racial/ethnic group [58].

Listening is an important aspect of rapport building with Native American patients, and practitioners should use active listening and reflective responses. Assessments and histories may include information regarding patients' stories, experiences, dreams, and rituals and their relevance. Interruptions and excessive questioning should be avoided if at all possible. Extended periods of silence may occur, and time should be allowed for patients to adjust and process information. Practitioners should avoid asking about family or personal matters unrelated to presenting issues without first asking permission to inquire about these areas. Native American patients often respond best when they are given suggestions and options rather than directions.

White American Patients

In 2021, 76.3% of the U.S. population identified as White alone [60]. The U.S. Census Bureau defines White race as person having origins in any of the original peoples of Europe, the Middle East, or North Africa [38]. While the proportion of population identifying as White only has decreased between 2010 and 2020, the numbers of persons identifying as White and another race/ethnicity increased significantly. The White population in the United States is diverse in its religious, cultural, and social composition. The greatest proportion of this group reports a German ancestry (17%), followed by Irish (13%), English (10%), and Italian (7%) [61].

Providers can assume that most well-accepted treatment approaches and interventions have been tested and evaluated with White American individuals, particularly men. However, approaches may need modification to suit class, ethnic, religious, and other factors.

Providers should establish not only the patient's ethnic background, but also how strongly the person identifies with that background. It is also important to be sensitive to persons multiracial/multiethnic heritage, if present, and how this might affect their family relationships and social experiences. Assumption of White race should be avoided, as White-passing persons of color have their own unique needs.

RELIGIOUS, CULTURAL, AND ETHNIC BACKGROUNDS

Religion, culture, beliefs, and ethnic customs can influence how patients understand health concepts, how they take care of their health, and how they make decisions related to their health. Without proper training, clinicians may deliver medical advice without understanding how health beliefs and cultural practices influence the way that advice is received. Asking about patients' religions, cultures, and ethnic customs can help clinicians engage patients so that, together, they can devise treatment plans that are consistent with the patients' values [37].

Respectfully ask patients about their health beliefs and customs and note their responses in their medical records. Address patients' cultural values specifically in the context of their health care. For example, one may ask [37]:

- "Is there anything I should know about your culture, beliefs, or religious practices that would help me take better care of you?"
- "Do you have any dietary restrictions that we should consider as we develop a food plan to help you lose weight?"
- "Your condition is very serious. Some people like to know everything that is going on with their illness, whereas others may want to know what is most important but not necessarily all the details. How much do you want to know? Is there anyone else you would like me to talk to about your condition?"
- "What do you call your illness and what do you think caused it?"
- "Do any traditional healers advise you about your health?"

Practitioners should avoid stereotyping based on religious or cultural background. Each person is an individual and may or may not adhere to certain cultural beliefs or practices common in his or her culture. Asking patients about their beliefs and way of life is the best way to be sure you know how their values may impact their care [37].

GENDER

Gender identity is a vital aspect of a person's experience of the world and of themselves. It also impacts the ways in which the world perceives and treats individuals, with a clear effect on the effective provision of health and mental health care. This section will focus on persons presenting as cisgender male or female; special considerations for those who are transgender, non-binary, or gender nonconforming will be explored in the next section.

An increasing amount of research is supporting a relationship between men's risk for disease and death and male gender identity, and the traditional male role has been shown to conflict with the fostering of healthy behaviors [62; 63]. Male gender identity is related to a tendency to take risks, and the predilection for risky behavior begins in boyhood [63; 64; 65]. In addition, boys are taught that they should be self-reliant and independent and should control their emotions, and societal norms for both boys and men dictate that they maintain a strong image by denying pain and weakness [62; 64; 65].

Issues related to male gender identity have several important implications for health. First, risky behavior is associated with increased morbidity and mortality. Second, the concept of masculinity leads to inadequate help- and information-seeking behavior and a reduced likelihood to engage in behavior to promote health [62; 64; 65]. These behaviors appear to be rooted in a decreased likelihood for men to perceive themselves as being ill or at risk for illness, injury, or death [62]. Third, male gender identity, coupled with lower rates of health literacy, creates special challenges for effectively communicating health messages to men [66; 67; 68]. Gender differences in health-related behaviors are consistent across racial/ethnic populations, although specific behaviors vary according to race/ethnicity [63].

Men's beliefs about masculinity and traditional male roles affect health communication, and healthcare practitioners should consider male-specific beliefs and perceptions when communicating with male patients. For example, because men tend to focus on present rather than future health, concepts of fear, wellness, and longevity often do not work well in health messages [69]. Instead, healthcare practitioners should focus more on "masculine" concepts, such as strength, safety, and performance, all of which tie into men's perceptions of their roles as providers and protectors.

Although men are more likely than women to lack a regular healthcare provider and to avoid seeking help or information, women are more likely to have a chronic condition requiring regular monitoring and are more likely to have forgone necessary health care due to the cost [70].

Providing gender-sensitive care to women involves overcoming the limitations imposed by the dominant medical model in women's health. This requires theoretical bases that do not reduce women's health and illness experience into a disease. This philosophy incorporates explanations of health and empowers women to effectively and adequately deal with their situations. The major components incorporated into the development of sensitive care include:

- Gender is a central feature.
- Women's own voices and experiences are reflected.
- Diversities and complexities are incorporated into women's experiences.
- Theorists reflect about underlying androcentric and ethnocentric assumptions.
- Sociopolitical contexts and constraints of women's experiences are considered.
- Guidelines for practice with specific groups of women are provided.

GENDER AND SEXUAL MINORITIES

The gender and sexual minority (GSM) population is a diverse group that can be defined as a subculture. It includes homosexual men, lesbian women, bisexual persons, transgender individuals, and those questioning their sexual identity, among others. The GSM population is diverse, representing all ages and all socioeconomic, ethnic, educational, and religious backgrounds. The population has been described as "hidden and invisible," "marginalized," and "stigmatized." As a result, the unique health and safety needs of the population have often been overlooked or ignored. Clear definitions of the concepts related to sexual identity will be helpful. The following is a glossary of terms used in discussions of this group [71; 72; 73; 74; 75; 76]:

Asexual/aromantic: An individual who does not experience sexual attraction. There is considerable diversity in individuals' desire (or lack thereof) for romantic or other relationships.

Bisexual: An adjective that refers to people who relate sexually and affectionately to both women and men.

Coming-out process: A process by which an individual, in the face of societal stigma, moves from denial to acknowledging his/her sexual orientation. Successful resolution leads to self-acceptance. Coming out is a lifelong process for lesbian, gay, bisexual, and transgender persons and their families and friends as they begin to tell others at work, in school, at church, and in their communities.

Gay: The umbrella term for GSM persons, although it most specifically refers to men who are attracted to and love men. It is equally acceptable and more accurate to refer to gay women as "lesbians."

Gender and sexual minorities (GSM): A term meant to encompass lesbian, gay, bisexual, trans, queer/questioning, intersex/intergender, asexual/ally (LGBTQIA) people as well as less well-recognized groups, including aromantic, two-spirited, and gender-fluid persons.

Heterosexism: An institutional and societal reinforcement of heterosexuality as the privileged and powerful norm.

Heterosexuality: Erotic feelings, attitudes, values, attraction, arousal, and/or physical contact with partners of the opposite gender.

Homophobia: A negative attitude or fear of non-straight sexuality or GSM individuals. This may be internalized in the form of negative feelings toward oneself and self-hatred. Called "internalized homophobia," it may be manifested by fear of discovery, denial, or discomfort with being LGBTQIA, low self-esteem, or aggression against other lesbians and gay men.

Homosexuality: The "persistent sexual and emotional attraction to members of one's own gender" as part of the continuum of sexual expression. Typically not used to describe people.

LGBTQIA: An acronym used to refer to the lesbian, gay, bisexual, transgender/transsexual, queer/questioning, intersex/intergender, asexual/ally community. In some cases, the acronym may be shortened for ease of use or lengthened for inclusivity. Members of this group may also be referred to as gender and sexual minorities (GSM).

Queer: An umbrella term to describe persons with a spectrum of identities and orientations that are outside of the heteronormative standard.

Sexual identity: The inner sense of oneself as a sexual being, including how one identifies in terms of gender and sexual orientation.

Sexual orientation: An enduring emotional, romantic, sexual, and/or affectionate attraction to another person. Individuals may experience this attraction to someone of the same gender, the opposite gender, both genders, or gender nonconforming.

Transgender: An umbrella term describing a number of distinct gender positions and identities including: crossdressing, transsexual, nonbinary, and intersex.

One's intrapersonal acceptance or rejection of societal stereotypes and prejudices, the acceptance of one's self-identity as a sexual minority, and how much one affiliates with other members of the GSM community varies greatly among individuals [77]. Some authors stress the diversity within the GSM community by discussing "GSM populations" [78]. For example, it is understandable that a GSM population living in rural areas of the United States would have little in common with a GSM population living in urban areas or "gay-friendly" neighborhoods. Additionally, mental health experts have suggested that "GSM community" symbolizes a single group of individuals who express their sexuality differently than the majority of heterosexual individuals. However, many distinct communities have been identified, including lesbian, gay, bisexual, and transgender [79]. Each community is different from the other as well as different from the heterosexual community. A culturally competent healthcare provider should keep this diversity in mind so that vital differences among these smaller groups are not lost when thinking of the GSM population in general.

Commonalities exist among the GSM communities as well. For example, many adolescents, whether gay, lesbian, bisexual, transgender, or questioning their sexual identity, lack sexual minority role models to assist with successful psychosocial development [79].

The subtle and pervasive ways that discomfort with GSM individuals may be manifested have been examined and, in some instances, categorized as "cultural heterosexism," which is characterized by the stigmatization in thinking and actions found in our nation's cultural institutions, such as the educational and legal systems [80]. "Cultural heterosexism fosters individual antigay attitudes by providing a ready-made system

of values and stereotypical beliefs that justify such prejudice as natural" [81]. Perhaps the paucity of information about the GSM community in basic professional education has been a reflection of cultural heterosexism. Writers, funding sources, and publishers have been exposed to the same cultural institutions for many years.

Individuals generally begin to absorb these institutional attitudes as children and may consequently develop "psychologic heterosexism," which may also manifest as antigay prejudice. Many individuals, as children, have little contact with someone who is openly gay and, as a result, may not be able to associate homosexuality with an actual person. Instead, they may associate it with concepts such as "sin," "sickness," "predator," "outsider," or some other negative characteristic from which the individual wants to maintain distance [81]. Psychologic heterosexism involves (among other factors) considering sexual identity and determining that one does not want to think further about it. The direction of this thinking is undeniably negative, resulting in an environment that allows antigay hostility [81]. The impact of antigay prejudice on the physical and mental health of members of the LGBTQIA community and their families should not be underestimated [82; 83].

Sexual minority individuals also are not immune to societal attitudes and may internalize negative aspects of the antigay prejudice experience. Anxiety, depression, social withdrawal, and other reactions may result [2; 84]. While the study of psychologic heterosexism, both blatant and subtle, is in the early stages of research, it has had a measurable impact on the mental health of the GSM community [85; 86; 87; 88].

Examples of the range of manifestations of heterosexism and/or homophobia in our society are readily available. Without difficulty, each example presented here may be conceptualized as related to the emotional or physical health of a GSM individual or family member:

- A kindergarten student calls another child an LGBTQ+ slur but does not really know what he is saying.
- A teenage girl allows herself to become pregnant, "proving" her heterosexuality to herself, her family, and her friends.
- A parent worries that her 12-year-old daughter is still a "tomboy."
- An office employee decides to place a photo of an old boyfriend in her office rather than a photo of her gender-nonconforming partner of five years.
- A college student buries himself in his studies in an effort to ignore his same-sex feelings and replace feelings of isolation.
- Two teenage girls, thought by peers to be transgender individuals, are assaulted and killed while sitting together in an automobile.
- A female patient is told by a healthcare provider that her haircut makes her look like a lesbian and is examined roughly.
- A gay man chooses not to reveal his sexual identity to his healthcare provider out of fear of a reduction or withdrawal of healthcare services.

The manifestations of heterosexism have inhibited our learning about the LGBTQIA population and its needs [78]. Gay patients have feared open discussion about their health needs because of potential negative reactions to their self-disclosure. Prejudice has impacted research efforts by limiting available funding [77]. All of these factors emphasize that the healthcare education system has failed to educate providers and researchers about the unique aspects of LGBTQIA health [83; 89].

Common Myths

Many myths surround homosexuality; a few are outlined below. The origin of these myths may be better understood after examining the history of homosexuality as well as the attitudes toward human sexuality in general. The history of the development of societal norms related to homosexuality includes misconceptions developed during times when research was not available on which to build a scientific knowledge base [82; 90; 91; 92].

Myth: Sexual orientation is a choice.

Fact: No consensus exists among scientists about the reasons that an individual develops his/her sexual orientation. Some research has shown that the bodies and brains of gay men and women differ subtly in structure and function from their heterosexual counterparts; however, no findings have conclusively shown that sexual orientation is determined by any particular factor or set of factors. Many people confuse sexual orientation with sexual identity. The reader may consider reviewing the definitions of these terms when further considering this myth.

Myth: Gay men and lesbians can be easily identified because they have distinctive characteristics.

Fact: Most gay and lesbian individuals conform to the majority of society in the way they dress and act. Further, a person's appearance is not necessarily an indication of sexual or romantic interests.

Myth: Gay individuals are child molesters.

Fact: This is a very damaging and heterosexist position. According to experts in the field of sexual abuse, the vast majority of those who molest children are heterosexual. The average offender is a White heterosexual man whom the child knows.

Myth: Gay people want to come into our schools and recruit our children to their "lifestyle."

Fact: Efforts to bring issues related to LGBTQIA history and rights into schools are not efforts to "convert," just as education on European history is not an effort to glamorize or "convert" to European identity. The intent has been to teach a more complete history of the world and to prevent children from mistreating LGBTQIA who are often the subjects of harassment and physical attacks. There is no evidence that people could be "recruited" to a gay sexual orientation, even if someone wanted to do this.

AGE

Elderly patients should be routinely screened for health and mental health conditions using tools specifically developed for this population, in spite of some practitioners' discomfort with asking questions about sensitive topics. These population-appropriate assessments may be included in other health screening tools [93].

Wellness and purpose have become important emphases when working with older adults [94]. In the past, aging was associated with disability, loss, decline, and a separation from occupational productivity. Although patient growth and positive change and development are values that practitioners embrace, the unconscious acceptance of societal myths and stereotypes of aging may prevent practitioners from promoting these values in elderly individuals [95].

Common Myths of Aging

Society holds several myths about the elderly. Many of these myths may be easily disputed based on data from the U.S. Census and other studies.

Myth: Most older adults live alone and are isolated.

Fact: In 2018, 70% of men and 46% of women 65 years and older were married. An estimated 28% lived alone [96]. According to a survey conducted in 2009, 9 out of 10 individuals 65 years of age and older stated they talked to family and friends on a daily basis [97]. In 2016, an estimated 20% of the U.S. population lived in a household comprised of two adult generations or a grandparent or at least one other generation, compared with 12% in 1980 [97; 98]. This multigenerational household trend particularly affects those 65 years and older, with 21% of these individuals living in multigenerational households in 2016. This group was second only to individuals 25 to 29 years of age (33%) [98]. Several factors have contributed to this trend, including growing racial and ethnic diversity and adults getting married later [97; 98].

Myth: Most older adults engage in very minimal productive activity.

Fact: In 2016, 18.6% of persons 65 years and older were employed or actively looking for work, and this population represents approximately 8% of the total labor force in the United States [99]. The elderly are more engaged in self-employed activities than younger persons. In 2016, 16.4% of those 65 years of age and older were self-employed, compared with an average of 5.5% of those 16 years to 64 years of age [100].

Myth: Life satisfaction is low among the elderly.

Fact: Data from the Berkeley Older Generation Study indicate that many elders are quite satisfied with their life [101]. More than one-third (36%) of persons older than 59 years of age and 15% of those older than 79 years of age stated they were currently experiencing the best time in their lives. A 2009 survey found that 60% of individuals 65 years of age and older stated they were very happy. A 2012 survey found that 65% of individuals 65 years of age and older indicated that the past year of their life has been normal or better than normal, and more than 80% of respondents agreed with the statement, "I have a strong sense of purpose and passion about my life and my future" [102]. Most of the factors that predict happiness for the young, such as good health and financial stability, also apply to the elderly. Older adults tend to report higher levels of well-being in part due to the quality of their social relationships [103].

PERSONS WITH MENTAL OR PHYSICAL DISABILITY

Americans with disabilities represent a large and heterogeneous segment of the population. The prevalence of disability varies by age group and definition. Based on the U.S. Census Bureau's 2013 American Community Survey (ACS), which describes disability in terms of functional limitations, 12.6% of the civilian U.S. noninstitutionalized population has a disability, defined as difficulty in hearing or vision, cognitive function, ambulation, self-care, or independent living [104]. The U.S. Department of Education, which uses categorical disability labels, estimates that 13% of children and youth 3 to 21 years of age have a disability (defined as specific learning disabilities, speech or language impairments, intellectual disability, emotional disturbance, hearing impairments, orthopedic impairments, other health impairments, visual impairments, multiple disabilities, deaf-blindness, autism, traumatic brain injury, or developmental delay) [104].

People with disabilities experience many health disparities. Some documented disparities include poorer self-rated health; higher rates of obesity, smoking, and inactivity; fewer cancer screenings (particularly mammography and Pap tests); fewer breast-conserving surgeries when breast cancer is diagnosed; and higher rates of death from breast or lung cancer [104].

Disability cultural competence requires appreciation of social model precepts, which recognize patients' rights to seek care that meets their expectations and values. The social model of disability has been characterized as centering disability as a social creation rather than an attribute of the patient [105]. As such, disability requires a social/political response in order to improve environmental factors affecting access and acceptance [105]. This involves adoption of person-first language, acknowledgement of social and environmental factors impacting persons abilities, and confronting disability-associated stigma.

VETERANS

The effects of military service and deployment to military combat on the individual and the family system are wide-reaching. According to the U.S. Department of Defense, there were 3.5 million current military personnel in 2020 and 18.3 million veterans in 2017 [132; 133]. The Army has the largest number of active duty members, followed by the Navy, the Air Force, and the Marine Corps [132]. Military service presents its own set of risk and protective factors for a variety of mental health issues, including post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), depression and suicide, substance abuse, and interpersonal violence. In particular, transitioning from combat back to home life can be particularly trying for veterans and their families.

As the number of military conflicts and deployments has increased since 2001, the need to identify and provide better treatment to veterans and their families has become a greater priority. The first step in providing optimal care is the identification of veterans and veteran families during initial assessments, with an acknowledgement that veterans may be any sex/gender and are present in all adult age groups [133].

Unfortunately, veterans and military families often do not voluntarily report their military service in healthcare appointments. In 2015, the American Medical Association updated its recommendations for social history taking to include military history and veteran status [134]. In addition, the American Academy of Nursing has designed the Have You Ever Served? Initiative to encourage health and mental health professionals to ask their patients about military service and related areas of concern [135]. This program provides pocket cards, posters, and resource links for professionals working with veterans and their families. Recommended questions for intake include [135]:

- Have you or has someone close to you ever served in the military?
- When did you serve?
- Which branch?
- What did you do while you were in the military?
- Were you assigned to a hostile or combative area?
- Did you experience enemy fire, see combat, or witness casualties?
- Were you wounded, injured, or hospitalized?
- Did you participate in any experimental projects or tests?
- Were you exposed to noise, chemicals, gases, demolition of munitions, pesticides, or other hazardous substances?

PROMOTING CULTURALLY SENSITIVE COMMUNICATION

Communication, the process of sending a message from one party to another, consists of both verbal and nonverbal components. Verbal and nonverbal communications are embedded within the culture of the parties disseminating the information and within the culture of the parties receiving the information. Communication is complex and multilayered because it involves unstated, implicit rules about a variety of factors, including physical distance between parties, tone of voice, acceptable topics of discussion, physical contact, and amount of eye contact [106]. Each of these variables is influenced by the perception of the level of formality/informality of the situation. Frequently, misunderstandings occur because the decoding and interpretation of these nonverbal cues are not accurate.

The verbal component of communication is just as complicated. Certainly, similarity in language shared by both parties enhances communication, but assuming that both parties in a conversation speak the same language, how the information is interpreted is still influenced by a host of factors. Linguists have posited that approximately 14,000 different meanings and interpretations can be extracted from the 500 most common English words [107]. Consequently, practitioners must be aware of the different communication styles held by diverse ethnic minority patients, as the clinical communication process is the primary vehicle by which problems and solutions are identified and conveyed [108].

Styles of communication can be classified from high- to low-context [109]. High-context cultures are those cultures that disseminate information relying on shared experience, implicit messages, nonverbal cues, and the relationship between the two parties [107; 110]. Members of these cultural groups tend to listen with their eyes and focus on how something was said or conveyed [106; 109]. On the other hand, low-context cultures rely on verbal communication or what is explicitly stated in the conversation [107]. Consequently, low-context communicators listen with their ears and focus on what is being said [106; 109; 110]. Western culture, including the United States, can be classified as a low-context culture. On the other hand, groups from collectivistic cultures, such as Asian/Pacific Islanders, Hispanics, Native Americans, and African Americans, are from high-context cultures [109].

Communicators from high-context cultures generally display the following characteristics [106; 107; 110; 111]:

- Use of indirect modes of communication
- Use of vague descriptions
- Less talk and less eye contact
- Interpersonal sensitivity
- Use of feelings to facilitate behavior
- Assumed recollection of shared experiences

- Reliance on nonverbal cues such as gestures, tone of voice, posture, voice level, rhythm of speaking, emotions, and pace and timing of speech
- Assimilation of the "whole" picture, including visual and auditory cues
- Emotional speech
- Use of silence
- Use of more formal language, emphasizing hierarchy between parties

On the other hand, low-context communicators can typically be described as [106; 107; 110]:

- Employing direct patterns of communication
- Using explicit descriptions and terms
- Assuming meanings are described explicitly
- Utilizing and relying minimally on nonverbal cues
- Speaking more and often raising their voices (more animated, dramatic)
- Often being impatient to get to the point of the discussion
- Using more informal language; less emphasis on hierarchy, more equality between parties (more friendly)
- Being more comfortable with fluidness and change
- Uncomfortable using long pauses and storytelling as a means of communicating

Understanding the distinctions between individuals who come from high- and low-context cultures can promote cultural sensitivity. However, it is vital that practitioners take heed of several words of caution. First, it is important not to assume that two individuals sharing the same culture (e.g., low-context culture) will automatically have a shared script for communicating. Second, it is important to not immediately classify an individual into a low- or high-context culture because of their ethnicity. A Chinese American man may not necessarily be a high-context communicator because he is Asian. A host of factors, such as level of acculturation, upbringing and socialization, education, and family immigration history, will all play a role in how one learns to communicate. Third, a major criticism of the discussion of low-/high-context cultures is that they reinforce dualism and ultimately oversimplify the complexities and nuances of communication [112].

Learning to communicate effectively also requires an understanding of how different conversational traits influence the communication process, or how information is conveyed and interpreted. Again, the goal of this section is not to simply dichotomize individuals' conversational styles into categories, but rather to understand the factors that play a role in how someone makes a decision on how to communicate [106].

As long as there are two parties involved in a conversation, nonverbal communication is inevitable, and it becomes salient particularly when it is processed from one culture to another. Nonverbal communication is any behavior (including gestures, posture, eye contact, facial expressions, and body positions) that transcends verbal or written forms of communication [113]. Nonverbal communication can enhance or reinforce what is said verbally, and conversely, it can completely contradict the message communicated verbally. It can also end up replacing what was verbally communicated if both parties do not share a native language [114].

In Western culture, communication is more direct and eye contact is highly valued. When eye contact is not maintained, many Westerners assume that the party is hiding pertinent information. However, in some cultures, reducing eye contact is a sign of respect [108]. Conversely, patients may interpret direct and indirect gazes differently. For example, in one study, Japanese individuals tended to rate faces with a direct gaze as angry and less pleasant compared with Finnish participants [115].

The amount of social space or distance between two communicating parties is culturally charged as well. Depending upon the social context, Westerners tend to maintain a distance of about three feet, or an arm's length, in conversations [107]. In a public setting, where both parties are engaged in a neutral, nonpersonal topic, Westerners will feel encroached upon and uncomfortable if an individual maintains a closer conversational distance. However, in other cultures, such as Latino and Middle Eastern, a closer distance would be the norm [107]. Chung recommends that in a clinical setting the practitioner allow patients to set the tone and social distance [116]. The practitioner can sit first and permit the patient to select where they want to sit.

Cross-cultural communication is by no means simple, and there is no set of rules to merely abide by. Instead, promoting culturally sensitive communication is an art that requires practitioners to self-reflect, be self-aware, and be willing to learn. Therefore, as practitioners become skilled in noticing nonverbal behaviors and how they relate to their own behaviors and emotions, they will be more able to understand their own level of discomfort and comprehend behavior from a cultural perspective [106].

CULTURALLY SENSITIVE ASSESSMENT GUIDELINES

Practitioners may be categorized as either disease-centric or patient-centric [117]. Disease-centered practitioners are concerned with sign/symptom observation and, ultimately, diagnosis. On the other hand, patient-centered practitioners focus more on the patient's experience of the illness, subjective descriptions, and personal beliefs [117]. Patient-centered practice involves culturally sensitive assessment. It allows practitioners to move assessment and practice away from a pathology-oriented model and instead acknowledge the complex transactions of the individual's movement within, among, and between various systems [118].

Practitioners who engage in culturally sensitive assessment nonjudgementally obtain information related to the patient's cultural beliefs, overall perspective, and specific health beliefs [119]. They also allow the patient to control the timing [120].

The goal is to avoid the tendency to misinterpret health concerns of ethnic minority patients. Panos and Panos have developed a qualitative culturally sensitive assessment process that focuses on several domains [119]. Each domain includes several questions a practitioner may address in order to ensure that he or she is providing culturally responsive care.

Alternatively, Kleinman suggests that the practitioner ask the patient what he or she thinks is the nature of the problem [121]. He highlights the following types of questions that may be posed to the patient [121]:

- Why has the illness/problem affected you?
- Why has the illness had its onset now?
- What course do you think the illness will follow?
- How does the illness affect you?
- What do you think is the best or appropriate treatment? What treatment do you want?
- What do you fear most about the illness and its treatment?

Similar to Kleinman's culturally sensitive assessment questions, Galanti has proposed the 4 Cs of Culture [122]:

- What do you call the problem?
- What do you think caused it?
- How do you cope with the problem?
- What questions or concerns do you have about the problem or treatment?

Pachter proposed a dynamic model that involves several tiers and transactions, similar to Panos and Panos' model [123]. The first component of Pachter's model calls for the practitioner to take responsibility for cultural awareness and knowledge. The professional must be willing to acknowledge that they do not possess enough or adequate knowledge in health beliefs and practices among the different ethnic and cultural groups they come in contact with. Reading and becoming familiar with medical anthropology is a good first step.

The second component emphasizes the need for specifically tailored assessment [123]. Pachter advocates the notion that there is tremendous diversity within groups. Often, there are many intersecting variables, such as level of acculturation, age at immigration, educational level, and socioeconomic status, that influence health ideologies. Finally, the third component involves a negotiation process between the patient and the professional [123]. The negotiation consists of a dialogue that involves a genuine respect of beliefs. The professional might recommend a combination of alternative and Western treatments.

Beckerman and Corbett further recommend that recently immigrated families be assessed for [124]:

- Coping and adaptation strengths
- Issues of loss and adaptation
- The structure of the family in terms of boundaries and hierarchies after immigration
- Specific emotional needs
- Acculturative stress and conflict for each family member

Practitioners should seek to understand the sociopolitical context of the origin country [125]. A migration narrative is also recommended, whereby an individual provides a story of their migration history. Asking about how long the family has been in the United States, who immigrated first, who was left behind, and what support networks are lacking gives the practitioner an overview of the individual's present situation [126]. The theme of loss is very important to explore. Types of losses may include family and friends left behind, social status, social identity, financial resources, and familiarity [126]. For refugees and newly immigrated individuals and families, assessment of basic needs (e.g., food, housing, transportation) is necessary [125].

Culturally sensitive assessment involves a dynamic framework whereby the practitioner engages in a continual process of questioning. Practitioners should work to recognize that there are a host of factors that contribute to patients' multiple identities (e.g., race, gender, socioeconomic status, religion) [127].

WELCOMING AND SAFE ENVIRONMENT

Improving access to care can be facilitated, in part, by providing a welcoming environment. The basis of establishing a safe and welcoming environment for all patients is security, which begins with inclusive practice and good clinician-patient rapport. Shared respect is critical to a patient's feeling of psychological well-being. Security can also be fostered by a positive and safe physical setting. For patients who are acutely ill, both the illness experience and treatment process can produce trauma. This is particularly true if involuntary detainment or hospitalization is necessary, but exposure to other individuals' narratives of experienced trauma or observing atypical behaviors from individuals presenting as violent, disorganized, or harmful to themselves can also be traumatic. As such, care environments should be controlled in a way to minimize traumatic stress responses. Providers should keep this in mind when structuring the environment (e.g., lighting, arrangement of space), creating processes (e.g., layout of appointments or care systems, forms), and providing staff guidance (e.g., nonverbal communication, intonation, communication patterns). During each encounter, the patient's perception of safety is impacted by caretakers and ancillary staff.

Experts recommend the adoption and posting of a nondiscrimination policy that signals to both healthcare providers and patients that all persons will be treated with dignity and respect [128]. Also, checklists and records should include options for the patient defining their race/ethnicity, preferred language, gender expression, and pronouns; this can help to better capture information about patients and be a sign of acceptance to that person. If appropriate, providers should admit their lack of experience with patient subgroups and seek guidance from patients regarding their expectations of the visit.

Front office staff should avoid discriminatory language and behaviors. For example, staff should avoid using gender-based pronouns, both on the phone and in person. Instead of asking, "How may I help you, sir?" the staff person could simply ask, "How may I help you?" Offices that utilize electronic health records should have a system to track and record the gender, name, and pronoun of all patients. This can be accomplished by standardizing the notes field to document a preferred name and pronoun for all patients [129]. Some persons who identify as non-binary (i.e., neither or both genders) may prefer that plural pronouns (e.g., they) be used.

Questions should be framed in ways that do not make assumptions about a patient's culture, gender identity, sexual orientation, or behavior. Language should be inclusive, allowing the patient to decide when and what to disclose. Assurance of confidentiality should be stressed to the patient to allow for a more open discussion, and confidentiality should be ensured if a patient is being referred to a different healthcare provider. Asking open-ended questions can be helpful during a history and physical.

The FACT acronym may be helpful for healthcare providers. Providers should:

- **F**ocus on those health issues for which the individual seeks care
- **A**void intrusive behavior
- **C**onsider people as individuals
- **T**reat individuals according to their gender

Training office staff to increase their knowledge and sensitivity toward persons will also help facilitate a positive experience for patients.

CONCLUSION

Culture serves as a lens through which patients and practitioners filter their experiences and perceptions. Patients will bring their unique life stories and concerns to the practitioner, and their cultural values and belief systems will inevitably shape how the problem is defined and their beliefs about what is effective in solving the problem. However, the cultural backgrounds and values of patients are not necessarily scripts that define behavior, and when practitioners view culture as a strength and not a pathology, practitioners will be able to more effectively join with patients to mobilize change.

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COURSE TEST - #97430 CULTURAL COMPETENCE: AN OVERVIEW

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

This 2 Hour activity must be completed by February 28, 2026.

1. A nurse acknowledges that she still has a lot to learn about different racial and ethnic minority groups. She is willing to learn from her patients and assume the role of learner. This nurse is demonstrating
- A) *diversity.*
- B) *reflexivity.*
- C) *explicit bias.*
- D) *cultural humility.*

2. Which of the following is NOT a risk factor in triggering implicit biases for health professionals?
- A) *Uncertainty*
- B) *Cognitive dissonance*
- C) *Time pressure to make a rapid decision*
- D) *Heavy workload and feeling behind schedule*

3. All of the following are categories of social determinants, EXCEPT:
- A) *Race*
- B) *Economic stability*
- C) *Health care access and quality*
- D) *Social and community context*

4. Which of the following has been identified as a core value of Black culture?
- A) *Spirituality*
- B) *Community*
- C) *Family/kinship*
- D) *All of the above*

5. Male gender identity is related to
- A) *risk avoidance.*
- B) *emotional demonstration.*
- C) *denying pain and weakness.*
- D) *teamwork and help-seeking.*

6. Cultural heterosexism is characterized by
- A) *negative feelings toward oneself and self-hatred.*
- B) *A negative attitude or fear of non-straight sexuality or GSM individuals.*
- C) *considering sexual identity and determining that one does not want to think further about it.*
- D) *the stigmatization in thinking and actions found in cultural institutions, such as educational and legal systems.*

7. Persons with disability experience higher rates of all of the following, EXCEPT:
- A) *Obesity*
- B) *Smoking*
- C) *Cancer screening*
- D) *Breast and lung cancer mortality*

8. Which of the following is a typical characteristic of communication in high-context cultures?
- A) *Use of more informal language*
- B) *Speaking more and often raising one's voice*
- C) *Assumption that meanings are described explicitly*
- D) *Reliance on interpreting eye contact, gestures, and tone of voice*

9. Which of the following is an attribute of patient-centered practice?
- A) *The practitioner focuses on observed signs and symptoms.*
- B) *The practitioner is concerned with identifying the disease pathology.*
- C) *The practitioner focuses on the subjective description of the illness.*
- D) *The practitioner is not influenced by how the client/patient defines the illness.*

10. The basis of establishing a safe and welcoming environment for all patients is
- A) *security.*
- B) *autonomy.*
- C) *beneficence.*
- D) *maintaining distance.*

Malaria and the International Traveler

This course meets the California requirement for travel medicine education for those who furnish these medications.

Audience
This course is designed for healthcare professionals involved in the care of persons traveling to or from areas where malaria transmission is common.

Course Objective
Malaria poses a particularly serious threat to U.S. travelers to endemic regions, and delayed diagnosis is a leading cause of death among patients with malaria in the United States. The purpose of this course is to provide healthcare professionals with the information necessary to accurately identify, treat, and educate patients regarding the risks of malaria in order to protect those who may be exposed to the disease.

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

1. Describe the history and natural life cycle of malaria.
2. Identify how and where the transmission of malaria occurs.
3. Differentiate between uncomplicated and severe (complicated) malaria and identify the symptoms of each.
4. Compare the methods used to diagnose malaria and review the importance of prompt diagnosis.
5. Recommend the appropriate treatment for malaria of various origins.
6. Identify the preventive measures against malaria that have been recommended, including presumptive self-treatment, and discuss considerations for non-English-proficient patients.

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Faculty Disclosure
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EVIDENCE-BASED PRACTICE RECOMMENDATION

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

INTRODUCTION

The symptoms of malaria were first described around 2700 B.C.E. in ancient Chinese medical writings [1]. Thousands of years later, malaria continues to be one of the most significant infectious diseases. Approximately 3.2 billion people live in areas of malaria transmission, and an estimated 150 to 300 million cases of malaria are reported each year. Malaria is a leading cause of illness and death in the developing world, killing an average of 600,000 people each year [2; 58]. Young children and pregnant women are the groups most affected [2; 37; 58]. Although the transmission of malaria was successfully interrupted in the United States during the late 1940s, it continues to pose a challenging health threat to individuals who travel to and emigrate from malarious areas [5; 54].

LIFE CYCLE OF MALARIA

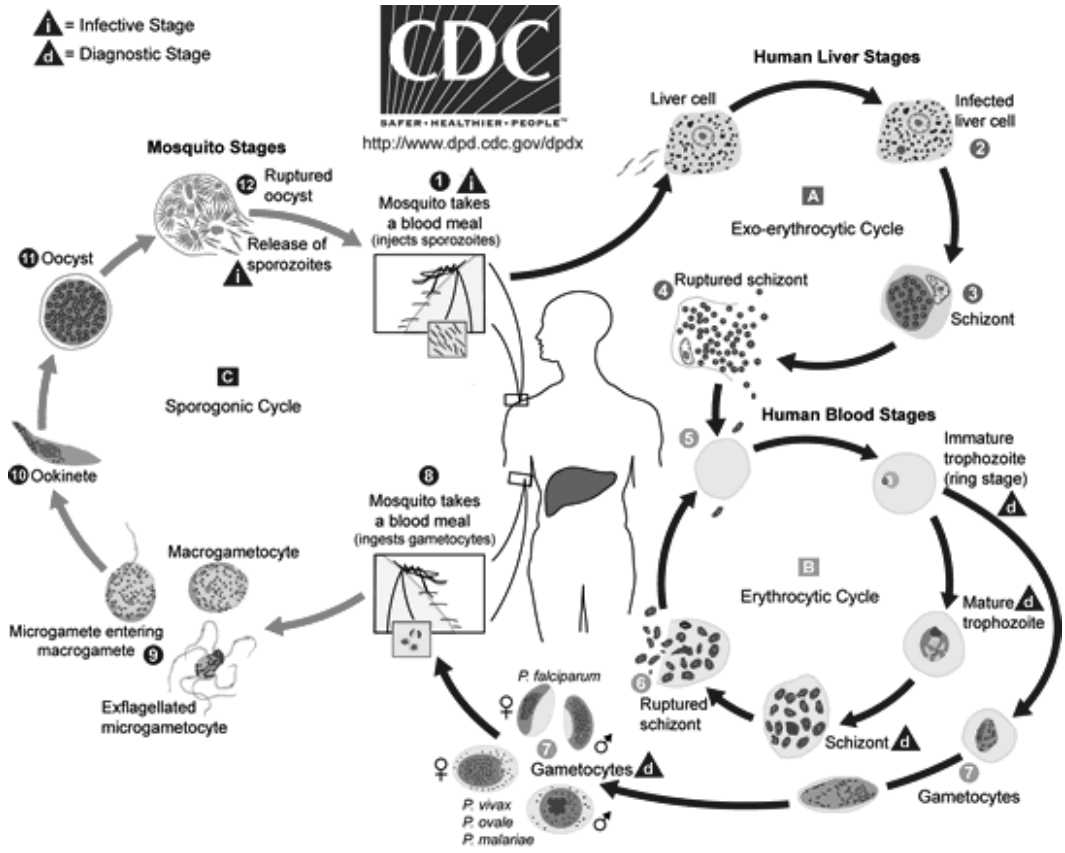
Malaria is a mosquito-borne disease caused by a parasite from the genus *Plasmodium*. Although there are more than 100 species of *Plasmodium*, only five are known to infect humans. These include *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and the more recently discovered *P. knowlesi* (a simian malaria parasite), which has previously been misdiagnosed in humans as *P. malariae* [6; 7; 8; 9; 26]. *P. falciparum* and *P. vivax* cause the most infections worldwide. *P. falciparum* is the agent of severe, potentially fatal malaria due to its unique ability to invade and multiply inside erythrocytes. If treated promptly and effectively, however, it is almost always curable. *P. vivax* is the most geographically widespread of the species. Although it produces symptoms that are less severe, relapses of infection caused by *P. vivax* may occur up to three years after the initial infection. *P. malariae* produces long-lasting infections that have the ability to persist asymptomatically for years. Occurrences of infection from *P. ovale* are rare and generally limited to West Africa [3; 10; 11]. Little is known about the morphology of *P. knowlesi* parasites, but they do appear to have unique characteristics that can be identified through the use of light microscopy [12]. *P. knowlesi* appears to cause less severe clinical disease than *P. falciparum*; however, it may cause more severe and potentially fatal infections than *P. vivax* or *P. malariae [6].* The severity of infection caused by *P. knowlesi* is the result of its rapid (i.e., 24-hour), targeted erythrocytic cycle. *P. knowlesi* is widespread throughout Malaysia, accounting for approximately 70% of human malaria infections in this area. Cases of infection with *P. knowlesi* have also been reported in Thailand, China, Singapore, and the Philippines [12; 26].

These malaria-causing parasites are carried and transmitted by the female *Anopheles* mosquito. As the mosquito takes a human blood meal, it injects the parasites as sporozoites (the invasive form of the parasites) [13]. The sporozoites travel to the liver, where they invade liver cells, grow, divide, and produce successive generations of parasites called merozoites. The merozoites exit the liver cells and continue the cycle by invading other red blood cells, replicating asexually, and releasing newly formed merozoites into the host bloodstream. Some of these infected cells leave the cycle of asexual replication and develop into male or female gametocytes, which continue circulating in the host bloodstream. When the gametocytes are ingested by the mosquito during a blood meal, another cycle of growth and multiplication in the mosquito is begun (***Figure 1***) [3; 10]. The success of this cycle depends on factors such as temperature, humidity, mosquito longevity, and individual host factors [3; 14].

TRANSMISSION

As discussed, malaria is transmitted to humans by the female *Anopheles* mosquito. Only 30 to 40 of the known *Anopheles* species are vectors and spread malaria. The *A. gambiae*, which exists exclusively in Africa, is one of the most efficient vectors and also one of the most difficult to control [3]. Malaria transmission may also occur through exposure to contaminated blood or tissue products or from mother to fetus; however, these instances are rare [10; 15].

THE LIFE CYCLE OF MALARIA



Source: [52] *Figure 1*

Malaria is transmitted in areas that allow the *Anopheles* mosquito to survive and multiply. This occurs mainly in tropical and subtropical areas where the temperature, humidity, and rainfall create an environment that allows malaria parasites to complete their growth cycle in the mosquitoes. Temperature is particularly critical to completion of the life cycle. For example, even within the areas where transmission is most common (i.e., tropical and subtropical regions), it does not occur at high altitudes, during cooler seasons in some areas, and in most desert areas. Transmission is most common in sub-Saharan Africa (85% of cases in 2018), with the highest case rates (69.9%) occurring among travelers returning from West Africa [15]. Although malaria has been eliminated in western Europe and the United States, the presence of the *Anopheles* mosquito in these regions poses a constant risk of reintroduction of the disease, especially in regions with temperate climates [2; 53].

The Centers for Disease Control and Prevention (CDC) began malaria surveillance in 1957. Since then, 63 outbreaks of locally acquired malaria have occurred [15]. The last outbreak, which consisted of eight cases, occurred in the United States in 2003 and was linked to a strain of the *P. vivax* parasite. Testing by the CDC indicated that the parasite originated in the Americas [17]. There was also one case of congenital malaria in 2004, also linked to the *P. vivax* parasite [59].

SYMPTOMS AND DIAGNOSIS

Following the infective mosquito bite, an incubation period of between 7 and 30 days usually passes before the first symptoms of disease appear. Shorter incubation periods are associated with *P. falciparum*; longer periods are characteristic of *P. malariae*. A string of recurrent attacks is typical and generally includes chills, fever, and sweating. In addition to these symptoms, headache, general malaise, fatigue, muscular pains, nausea, vomiting, and diarrhea are also common [3; 10; 18].

Although infrequently observed, a classical attack of "uncomplicated" malaria lasts from 6 to 10 hours and recurs either every second or third day, depending on the infectious *Plasmodium* species. Additional physical findings may include weakness, an enlarged spleen or liver, mild jaundice, and an increased respiratory rate. Laboratory results may indicate mild anemia, thrombocytopenia, elevated bilirubin, aminotransferases, and albuminuria and the presence of urinary casts [3; 18].

Malaria infections with *P. falciparum* are categorized as severe when complicated by serious organ failure or abnormalities in the patient's blood or metabolism. Severe malaria occurs most frequently in persons either with no immunity or decreased immunity to the disease. The presence of one or more of the following clinical criteria indicates severe malaria [3; 4]:

- Seizures or other neurologic abnormalities
- Impaired consciousness or coma
- Abnormal behavior
- Severe normocytic anemia
- Pulmonary edema
- Acute respiratory distress syndrome
- Circulatory shock
- Disseminated intravascular coagulation
- Spontaneous bleeding
- Acidosis
- Hypoglycemia
- Hemoglobinuria
- Jaundice
- Acute kidney failure
- Repeated generalized convulsions
- Parasitemia greater than 5%

Severe illness is a medical emergency requiring urgent, aggressive treatment [3].

Prompt diagnosis of malaria is important to ensure timely treatment and prevent the spread of infection. Malaria may be suspected based on the patient's symptoms, travel history, and physical findings at examination. Patients with suspected infection should be urgently and thoroughly evaluated. Delayed diagnosis is a leading cause of death among patients with malaria in the United States [3]. It is important, however, that treatment not begin until the diagnosis has been confirmed with specific diagnostic tests (e.g., microscopy or rapid diagnostic tests) that help identify the type of infectious parasite and determine the severity of the infection. Identification of these factors will help the clinician determine the appropriate course of treatment [18; 19].

The criterion standard of microscopic diagnosis involves examination of thick and thin blood smears. (Thick smears are more sensitive but more difficult to read.) The smears are stained, usually with the Giemsa stain, which gives the parasites a distinctive appearance. A negative blood smear usually indicates no presence of infection. However, because nonimmune individuals may be symptomatic at very low parasite densities that are initially undetectable, the CDC has recommended that smears be repeated every 12 to 24 hours for 48 to 72 hours [4; 19; 20].

Alternative methods for laboratory diagnosis include immunologic tests to detect antigens derived from malaria parasites [18; 21]. These rapid diagnostic tests (RDTs) provide results within minutes and may be used where reliable microscopic diagnosis is not available. In 2007, the U.S. Food and Drug Administration (FDA) approved the first RDT for use in the United States. Because RDTs cannot confirm the species of malaria, the CDC has recommended that all RDT results be confirmed with microscopy [4;19; 22]. Due to recent improvements in quality and cost-effectiveness, RDTs are becoming more common in areas with little access to microscopy services [2; 27]. Polymerase chain reaction (PCR) may be used to detect parasite nucleic acids. Although it is a more sensitive and accurate diagnostic tool than microscopy, PCR is not a useful tool for diagnosing the acutely ill patient, primarily because of the time required to obtain results [4; 19].

Diagnosis of malaria may be difficult, and misdiagnosis is a common problem, particularly in areas where malaria is not endemic, like the United States. In areas where malaria is endemic, diagnosis may be difficult because intense transmission allows some individuals to develop immunity that protects them against illness but not infection. Healthcare providers should obtain a travel history from every febrile patient and should routinely suspect malaria in a patient who has recently traveled to an area with known malaria transmission [4; 5; 15; 19].

Malaria is a reportable disease in the United States and is included in the National Notifiable Diseases Surveillance System [23]. The CDC has recommended that healthcare providers report all cases of laboratory-confirmed malaria to their local or state health departments. These reports are then transmitted to the CDC for surveillance, prevention, and reporting purposes. Information about how to report a case of malaria, as well as reporting forms, are available from the CDC at https://www.cdc.gov/malaria/report.html [24].

TREATMENT

As previously stated, treatment of malaria should not be initiated until the diagnosis has been confirmed by laboratory analysis. After the diagnosis has been confirmed, treatment should begin immediately and be guided by the infecting *Plasmodium* species, the drug susceptibility of the infecting parasites, the geographical location (if known) of infection, and the patient's clinical status [4; 10].

EVIDENCE-BASED PRACTICE RECOMMENDATION

After the diagnosis of malaria has been made, appropriate antimalarial treatment must be initiated immediately. The Centers for Disease Control and Prevention recommend that treatment be guided by three main factors:

- The infecting *Plasmodium* species
- The clinical status of the patient
- The drug susceptibility of the infecting parasites as determined by the geographic area where the infection was acquired
- Previous use of antimalarials

(https://www.cdc.gov/malaria/resources/pdf/treatment_guidelines_101819.pdf. Last accessed September 22, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Determination of the infecting species is important because *P. falciparum* infections may progress rapidly and lead to severe illness or death. They therefore require urgent initiation of the appropriate therapy. *P. vivax* and *P. ovale* infections require specific, additional treatment because they produce dormant liver-stage parasites that are capable of causing relapses. *P. falciparum* and *P. vivax* species have demonstrated drug resistance patterns that vary by geographic region. Identification of the infecting species as well as knowledge of the geographic area where the infection was acquired can provide information about the drug resistance pattern of the infecting parasite and enable the clinician to choose an appropriate drug regimen and course of treatment [4]. Knowledge of drug resistance patterns is vital to the development and discovery of new antimalarial drugs [25].

The CDC has indicated that oral antimalarial drugs are an effective treatment choice for patients diagnosed with uncomplicated malaria. More severe disease requires aggressive treatment with parenteral antimalarials [4].

TREATMENT OF UNCOMPLICATED MALARIA

An oral antimalarial regimen is an effective choice for uncomplicated malaria; severe illness requires aggressive management and (initially) parenteral therapy. The CDC provides treatment of malaria guidelines for clinicians based on drug options available in the United States [4]. The CDC guidelines may be accessed online at https://www.cdc.gov/malaria/diagnosis_treatment/clinicians1.html, with treatment tables available at https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table.pdf. The CDC also maintains a malaria hotline at (855) 856-4713 or (770) 488-7100 for after-hours, weekends, and holidays.

Table 1 contains a summary of the CDC treatment recommendations for uncomplicated malaria. For cases in which the diagnosis or the infecting species has not yet been confirmed, treatment against *P. falciparum* should begin immediately and should include continuous monitoring of the patient's clinical status. Blood smears should be made to confirm an adequate response to treatment of infections with *P. falciparum* or suspected chloroquine-resistant *P. vivax* [4].

Relapses may occur in patients in whom either *P. vivax* or *P. ovale* are the infectious agent because, as noted, these agents have dormant liver-stage parasites capable of reactivating. Relapses may occur months to years after the initial infection and may or may not have associated symptoms. Therefore, for infections subsequently diagnosed as *P. vivax* or *P. ovale*, treatment with primaquine should be administered to prevent relapse. The CDC recommends 30 mg primaquine phosphate by mouth once daily for 14 days [4]. It is important to note that primaquine may cause hemolytic anemia in persons with glucose-6-phosphate-dehydrogenase (G6PD) deficiency; therefore, patients (including pediatric patients) should be screened for G6PD deficiency prior to commencement of treatment. Primaquine is contraindicated during pregnancy [3; 4].

Treatment without the benefit of laboratory confirmation ("presumptive" treatment) should be initiated only in extreme circumstances, such as strong clinical suspicion of infection, indications of severe disease, or the inability to obtain prompt confirmation via laboratory investigations [4]. The CDC has additionally recommended presumptive treatment of *P. falciparum* malaria in persons emigrating from Sub-Saharan Africa prior to their entry into the United States or postarrival, in certain instances [63]. This strategy is designed to decrease the risk of complications or death in a population that might lack access to health care. It is also designed to prevent existing infections from progressing to severe disease and reduce the risk of reintroduction of malaria into the United States [15].

TREATMENT DURING PREGNANCY

Malaria infection during pregnancy has been associated with high risks to both mother and fetus, including miscarriage, premature delivery, low birth weight, congenital infection, and maternal and perinatal morbidity and mortality. The reasons for these risks are poorly understood but may include a reduced maternal immune response that ineffectively clears the malaria infection. This is compounded by the ability of the malaria parasites to sequester and replicate in the placenta. Pregnant women are three times more likely than nonpregnant women to develop severe malaria [4]. Healthcare providers should counsel nonpregnant women of childbearing age to use contraception and avoid pregnancy during, and for up to three months following, treatment for malaria [4].

TREATMENT RECOMMENDATIONS FOR UNCOMPLICATED MALARIA			
***Plasmodium* species**	**Drug**	**Dosing**	**Comments**
P. falciparum or "species not identified" in areas **without** chloroquine-resistant strains	Chloroquine	Initial oral dose: 600 mg base (1,000 mg salt), followed with 300 mg base (500 mg salt) at 6, 24, and 48 hours Maximum dose: 1,500 mg base (2,500 mg salt)	Use adult dosing in pregnancy. Adjust pediatric dosing by patient weight; do not exceed recommended adult dosing. Consider atovaquone-proguanil (preferred) or mefloquine if quinine is unavailable. Quinine and atovaquone-proguanil are recommended for use in children 8 years of age and younger.
	Hydroxychloroquine (Second-line alternative)	Initial oral dose: 620 mg base (800 mg salt), given immediately, followed with 310 mg base (400 mg salt) at 6, 24, and 48 hours Maximum dose: 1,550 mg base (2,000 mg salt)	
P. falciparum or "species not identified" in areas **with** chloroquine-resistant strains (choose one of the following four options AND prescribe antirelapse treatment)	Atovaquone/proguanil	Adults: 1 g/400 mg dose, once daily for three days Available as 250 mg/100 mg adult tablets and 62.5 mg/25 mg pediatric tablets	These are fixed-dose combination medicines that may be used for nonpregnant adult and pediatric patients. Both have been found to be very effective. Adjust pediatric dosing by patient weight.
	Artemether/lumefantrine	Available as 20 mg/120 mg tablets. Three day, four dose course: Initial dose at hour 0 and second dose at hour 8, then one dose on days 2 and 3 5–<15 kg: 1 tablet per dose 15–<25 kg: 2 tablets per dose 25–<35 kg: 3 tablets per dose ≥35 kg (and adults): 4 tablets per dose	
	Quinine sulfate[a] (plus doxycycline, tetracycline, or clindamycin)	648 mg (i.e., 2 capsules) every eight hours for three to seven days	Clindamycin should be used in pregnancy and for children <8 years old
	Mefloquine	Three tablets (750 mg dose) at 0 hours followed by two tablets (500 mg dose) at 6–12 hours	Use only when other options are unavailable.
	Antirelapse treatment: Primaquine or tafenoquine	Primaquine 30 mg oral daily for 14 days, OR one oral dose of tafenoquine 300 mg	—
P. vivax or *P. ovale* acquired in all areas **except** Papua New Guinea or Indonesia (choose one of the two options AND prescribe antirelapse treatments)	Chloroquine	Same as for *P. falciparum*	If patient is nonresponsive, change treatment to one of the three options listed for treatment of *P. vivax* or *P. ovale* malaria acquired in Papua New Guinea and notify state health department and the CDC.
	Hydroxychloroquine (Second-line alternative)		
	Antirelapse treatment: Primaquine or tafenoquine	Primaquine 30 mg oral daily for 14 days, OR one oral dose of tafenoquine 300 mg	—

Table 1 continues on next page.

TREATMENT OF SEVERE MALARIA

Of the 1,800 cases of malaria diagnosed in the United States each year, approximately 10% are cases of severe malaria that carry an increased risk of death [28]. Because most deaths from severe malaria occur within the first 24 to 48 hours, patients with manifestations of severe malaria (including pregnant women) should be treated aggressively with parenteral antimalarial therapy as soon as possible after the diagnosis has been made [4]. If laboratory diagnosis cannot be immediately made, but severe malaria is strongly suspected, blood should be collected for diagnostic testing and empiric treatment started. Oral antimalarial drugs are not recommended for the

TREATMENT RECOMMENDATIONS FOR UNCOMPLICATED MALARIA			
P. vivax or *P. ovale* acquired in Papua New Guinea or Indonesia (choose one of the following four options AND prescribe antirelapse treatment)	Chloroquine	Same as for *P. falciparum*	If patient is nonresponsive, change treatment to one of the three options listed for treatment of *P. vivax* malaria acquired in Papua New Guinea and notify state health department and the CDC.
	High possibility of chloroquine-resistant strains.	Same as for *P. falciparum*	
P. vivax or *P. ovale* acquired in Papua New Guinea or Indonesia (choose one of the following four options AND prescribe antirelapse treatment) High possibility of chloroquine-resistant strains	Atovaquone/proguanil	Same as for *P. falciparum* in areas with chloroquine-resistant strains	These are fixed-dose combination medications that may be used and are effective for nonpregnant adult and pediatric patients.
	Artemether/lumefantrine		
	Mefloquine		
	Quinine sulfate[a] (plus doxycycline, tetracycline, or clindamycin)		Clindamycin should be used in pregnancy and for children <8 years old
	Mefloquine		Use only when other options are unavailable.
P. malariae or *P. knowlesi*	Any of the antimalarial regimens above may be prescribed; antirelapse treatment is not required. Mefloquine should only be use in the absence of other options.	For specific dosing, see above.	There is little evidence comparing various medications for the treatment of *P. knowlesi.*
[a]Pediatric dosing may require compounding.			
Source: [4; 12; 31]			*Table 1*

TREATMENT RECOMMENDATIONS FOR SEVERE MALARIA		
The regimen for the treatment of severe malaria in the United States consists of intravenous (IV) artesunate and, if infected with *P. vivax* or *P. ovale*, antirelapse therapy.		
Drug	**Dosing**	**Comments**
Artesunate	IV dose: 2.4 mg/kg IV doses: 0, 12, and 24 hours (3 total)	If IV artesunate is not immediately available, patients should be started on oral antimalarials: artemether/lumefantrine (preferred); or atovaquone-proguanil; or quinine sulfate; or mefloquine (only if no other options available). Antirelapse treatment should include one of either primaquine or tafenoquine. Dosing for all oral agents, including antirelapse treatment, is the same as for uncomplicated malaria (***Table 1***).
Source: [4]		*Table 2*

initial treatment of severe malaria unless the recommended medication, intravenous (IV) artesunate, is not immediately available [3; 4]. The treatment recommendations for patients with severe malaria are summarized in ***Table 2***.

Quinidine gluconate, an antiarrhythmic drug with antimalarial action, was previously the only parenterally administered antimalarial drug available in the United States. However, the marketing of quinidine was discontinued by the manufacturer in March 2019 [60]. In 2020, parenteral artesunate (from the

class of medications known as artemisinins) was approved to treat severe malaria in adult and pediatric patients [60]. The CDC and the World Health Organization (WHO) now recommended artesunate for the treatment of severe malaria [4; 28]. Intravenous artesunate is indicated for all patients with severe malaria disease, regardless of infecting species, [4; 28]. If artesunate cannot be obtained commercially within 24 hours, it can be obtained directly from the CDC by calling the malaria hotline [4].

A full course of oral therapy (artemether/lumefantrine is preferred) should follow the initial IV course if parasite density is ≤1% and the patient can tolerate oral medication. If parasite density is >1% after the first three doses of IV artesunate or if the patient cannot tolerate oral medications, they should be given the recommended IV dose once per day until the density is ≤1% (for a maximum of seven days) or until they can tolerate oral medications. Artesunate is safe in infants, children, and in the second and third trimesters of pregnancy. In the first trimester of pregnancy, no harmful effects have been observed (limited clinical data), and the CDC advises that the benefit of IV artesunate outweighs the risk to the patient and fetus [4]. Individuals administered IV artesunate should be monitored weekly for four weeks for evidence of hemolytic anemia.

Previously, the CDC recommended that exchange transfusion (e.g., the removal of infected red blood cells) be strongly considered for persons with a parasite density of more than 10%. It was also considered if the patient has complications, such as cerebral malaria, acute respiratory distress, or renal complications. However, exchange transfusion has not been proven beneficial in an adequately powered randomized controlled trial. In 2013, the CDC conducted an analysis of cases of severe malaria treated with exchange transfusion and was unable to demonstrate a survival benefit of the procedure. As a result, the CDC no longer recommends the use of exchange transfusion as an adjunct procedure for the treatment of severe malaria [4].

Reports of the emergence of parasites that are resistant to artemisinin derivatives are considered a threat to the global effort to control and eliminate malaria, and WHO has taken steps to confirm and contain such strains [2].

PREVENTION

Between 1997 and 2006, more than 10,000 cases of malaria among U.S. residents were reported to the CDC. The vast majority of these cases (86.8%) were acquired as a result of travel outside the United States [35]. In 2018, 1,823 cases were reported in the United States, with all except two resulting from international travel or immigration; one case resulted from a bone marrow transplant and another case was cryptic (i.e., unidentified) [3; 15]. Cases have been increasing in the United States since 1970, with an apparent peak in 2017. Travelers to sub-Saharan Africa are at greatest risk of acquiring a fatal malarial infection [15; 29; 32]. Although malaria poses a serious threat to travelers, it is preventable in most cases [33].

Malaria prevention consists of a combination of infection prevention (including personal protection) and chemoprophylaxis among persons at risk. It also includes assessing the risk factors for individual travelers and identifying appropriate preventive measures based upon that assessment. Travelers to malaria-endemic areas who have previously acquired malaria should be reminded that it may be acquired more than once [30; 33].

There is no criterion standard for assessing a traveler's risk of contracting malaria, so it is important that pre-travel guidance be obtained from a healthcare professional experienced in travel medicine. The level of risk and the individual traveler's profile will guide decision making in determining appropriate preventative measures [30; 34].

RISK ASSESSMENT

Factors to consider and include in a traveler's profile include knowledge about the traveler's destination, the season during which travel will occur, how and for how long the individual will travel, and the traveler's basic personal history. It is important to know the traveler's destination because the risk of acquiring malaria is not uniformly distributed throughout all countries; it may be confined to small areas in some countries. The season of travel is also important because temperature and rainfall may affect malaria transmission. The traveler's anticipated accommodations and activities should also be included in the risk assessment. Indoor accommodations, for example, may be less risky to the traveler than outdoor (e.g., camping) accommodations. Additionally, if the traveler expects to participate in outdoor evening activities, this will increase the risk of exposure to the infecting mosquito. The CDC has found that the greatest risk is among first- and second-generation immigrants who live in non-malaria-endemic countries and then return to their countries of origin to visit family and friends. Because many of these individuals incorrectly consider themselves to be immune, they forego pre-travel preventive measures [30; 33; 34].

The WHO has compiled a convenient ABCDE memory aid for travelers [55]:

- Be **aware** of the risk, the incubation period, and the main symptoms.
- Avoid being **bitten** by mosquitoes, especially between dusk and dawn.
- Take antimalarial drugs **(chemoprophylaxis)** to suppress infection where appropriate.
- Immediately seek **diagnosis** and treatment if a fever develops one week or more after entering an area where there is a malaria risk and up to three months after departure.

- Avoid outdoor activities in **environments** that are mosquito breeding places, such as swamps or marshy areas, especially in late evenings and at night.

PERSONAL PROTECTIVE MEASURES

The CDC and the Infectious Diseases Society of America have recommended that individuals traveling outside the United States be aware of and employ the following personal protective measures [30; 33]:

- Avoid travel to known malaria-endemic areas, when possible. Check https://wwwnc.cdc.gov/travel for updates on regional disease transmission patterns and outbreaks.
- Be aware of peak exposure times and places, usually outdoors at dawn and dusk.
- Wear clothing that minimizes skin exposure (e.g., long sleeves, pants, hats, boots).
- Use bed nets and ensure that they completely cover the sleeping area (e.g., down to the floor or tucked under the mattress). Nets pretreated with pyrethroid insecticides or repellents may be purchased prior to travel. Nets may also be treated after purchase.
- Use insecticides (with caution and as directed). *N,N*-diethyl-meta-toluamide (DEET) is an ingredient in many commercially available products and has historically been the most effective repellent; however, any EPA-registered repellant will be equally effective if used correctly. Metofluthrin and allethrin insecticides and spatial repellants (e.g., aerosol sprays, coils, vaporizing mats) are also recommended by the CDC to clear rooms of mosquitoes.

CHEMOPROPHYLAXIS

According to the WHO, more than 10,000 travelers become ill with malaria each year, despite the fact that malaria in travelers is usually preventable [29]. Most cases of malaria acquired due to travel occur because of "poor adherence to, or complete failure to use medicines, or use of inappropriate prophylactic malaria drug regimens, combined with failure to take adequate precautions against mosquito bites" [29]. A CDC surveillance summary of cases of malaria in patients with onset of illness in 2018 found that only 5% of these patients had adhered to or took a region-appropriate regimen of chemoprophylaxis [15].

In addition to the personal protective measures previously discussed, malaria prophylaxis is an important prevention component [15]. All travelers to malaria-endemic areas should take an antimalarial drug. Drug recommendations depend upon the country of travel. Up-to-date recommendations may be found on the CDC Traveler's Health website at https://wwwnc.cdc.gov/travel.

Travelers should be reminded that no antimalarial drug regimen is 100% protective and that it should always be combined with the personal protective measures, as discussed. The CDC has compiled a list of drugs for consideration in those instances when more than one drug has been recommended for a specific area (***Table 3***). Travelers should also be cautioned to be alert for counterfeit antimalarial drugs, which may contain either none or less than the required amount of the active ingredient(s). Some of these counterfeits have reportedly led to deaths [36]. Precautions that all travelers should employ when buying antimalarial drugs include [36]:

- Buying them in their home country before travel begins
- Carrying the manufacturer's name and the drug names (generic and brand) with them in case an additional supply is needed
- Inspecting the drug's packaging carefully and ensuring that it is intact
- Being suspicious of drugs that have a peculiar odor, taste, or color. Additional information about counterfeit drugs may be found on the FDA website.

PRESUMPTIVE SELF-TREATMENT

Malaria may be effectively treated early in the course of the disease; however, delay of appropriate treatment may have serious, even fatal, consequences. Travelers who choose not to take an antimalarial drug, who are on a less than effective regimen (e.g., chloroquine in a chloroquine-resistant risk area), whose medical history dictates a suboptimal drug, or who may be traveling to very remote areas may be prescribed a presumptive self-treatment course (***Table 4***). Travelers should be advised to take the treatment promptly if fever, chills, or other influenza-like illness occurs. This is particularly important if the traveler is unable to access professional medical care within 24 hours. Travelers should also be advised to seek medical care as soon as possible after self-treatment [15; 35].

INFECTION AND DISEASE PREVENTION

Infection may be prevented when the offending mosquitoes are prevented from biting humans. The three most common methods of prevention include insecticide-treated bed nets, intermittent preventive treatment of malaria in pregnant women, and indoor residual spraying [37].

Insecticide-Treated Bed Nets

Insecticide-treated bed nets have been shown to effectively reduce illness, disease, and death caused by malaria. They can reduce overall child mortality by as much as 20% and have additionally been shown to reduce the intensity of transmission [38; 39]. Because mosquitoes are able to feed through nontreated nets and those with even the tiniest holes or tears, the application of insecticides to bed nets improves protection significantly by repelling mosquitoes. Additionally, in communities where insecticide-treated nets are widely used, an overall reduction in the mosquito population has been found to occur.

CHOOSING A MALARIA PROPHYLAXIS REGIMEN FOR TRAVELERS		
Drug Option	**Benefits**	**Risks/Contraindications**
Atovaquone/ proguanil	May be started one to two days before traveling to a malaria-endemic area Must only be continued for seven days after traveling, rather than four weeks Very well tolerated medicine Pediatric tablets are available and may be more convenient	Contraindicated in women who are pregnant or breastfeeding a child who weighs less than 5 kg Contraindicated in patients with severe renal impairment Tends to be more expensive than some of the other options Some patients would rather not take a daily medication
Chloroquine	Taken only weekly Some patients (e.g., those with chronic rheumatologic conditions) may already be taking hydroxychloroquine Can be used in all trimesters of pregnancy	Cannot be used in areas with chloroquine or mefloquine resistance May exacerbate psoriasis Must continue taking medication for four weeks after travel Must be started one to two weeks prior to travel
Doxycycline	May be started one to two days before traveling to a malaria-endemic area Tends to be the least expensive antimalarial Patients may already be taking doxycycline chronically for prevention of acne Doxycycline can also prevent some additional travel-related infections (e.g., *Rickettsia* and leptospirosis), particularly if patients plan to hike, camp, or swim in fresh water	Contraindicated for pregnant women and children younger than 8 years of age Some patients would rather not take a daily medication Must continue taking medication for four weeks after travel Long-term antibiotic use can increase the risk of fungal overgrowth Increased risk of sun sensitivity and gastrointestinal side effects
Mefloquine	Taken only weekly Can be used in the second and third trimester of pregnancy and in the first trimester if there is no other option (e.g., postpone travel)	Contraindicated for travel to areas with mefloquine resistance and in patients with seizure disorders and certain psychiatric conditions Not recommended for patients with cardiac conduction abnormalities Must be started at least two weeks prior to travel and continued for four weeks after return
Primaquine	The most effective medication for preventing *P. vivax* May be started one to two days before traveling to a malaria-endemic area Must only be continued for seven days after traveling, rather than four weeks	Contraindicated in patients with glucose-6-phosphatase dehydrogenase (G6PD) deficiency or whose G6PD deficiency status is unknown Contraindicated in pregnant women and women who are breastfeeding, unless the infant has also been tested for G6PD deficiency Increased risk for gastrointestinal side effects
Tafenoquine	One of the most effective drugs for prevention of *P. vivax* malaria, but also prevents *P. falciparum* May be appropriate for shorter trips (taken once, one week after traveling) or for last-minute travel (started three days before traveling to an endemic area)	Contraindicated in patients with glucose-6-phosphatase dehydrogenase (G6PD) deficiency, nor those who have not been tested for G6PD deficiency Contraindicated in children and women who are pregnant or breastfeeding Not recommended for those with psychotic disorders
Source: [47]		*Table 3*

PRESUMPTIVE SELF-TREATMENT WITH ATOVAQUONE/PROGUANIL[a]		
Patient	**Dose**	**Comments**
Adult	Four tablets (1,000 mg atovaquone and 400 mg proguanil each) orally as a single daily dose for three consecutive days	Not currently recommended for pregnant women and women breastfeeding infants weighing less than 5 kg Contraindicated in persons with severe renal impairment
Child 5–8 kg	Two pediatric tablets (62.5 mg atovaquone and 25 mg proguanil each)	Not currently recommended for children <5 kg
Child 9–10 kg	Three pediatric tablets	
Child 11–20 kg	One adult tablet	
Child 21–30 kg	Two adult tablets	
Child 31–40 kg	Three adult tablets	
Child ≥41 kg	Four adult tablets	
[a]Self-treatment should be initiated if professional medical care is not available within 24 hours. Medical care should be sought immediately after treatment.		
Source: [30; 35]		*Table 4*

Long-lasting insecticide-treated nets have also been developed. They offer significant maintenance and use advantages over the older nets, which had to be retreated frequently. The long-lasting insecticide-treated nets offer protection for up to three years. The WHO has recommended several long-lasting insecticide-treated nets [40]:

- Interceptor G2 (BASF)
- Olyset Plus (Sumitomo Chemical)
- PermaNet 3.0 (Vestergaard-Frandsen)
- Royal Guard (Disease Control Technologies)
- Tsara Boost (NRS Moon Netting)
- Tsara Plus (NRS Moon Netting)
- Veeralin (VKA Polymers Private Limited)
- Infection and Disease Prevention During Pregnancy

As previously discussed, malaria can have severe, even fatal consequences for a pregnant woman and her fetus. Women who are having their first or second pregnancy and women who are HIV-positive are at an increased risk. The effects of malaria infection on the pregnant woman and her fetus have been found to vary according to the area of transmission. These effects range from maternal anemia, acute respiratory distress, and low-birth-weight infants (generally in areas of high transmission) to severe disease, premature delivery, and even fetal loss (generally in areas of low transmission) [41]. Intermittent preventive treatment involves administration of a full course of an antimalarial at specified intervals (generally two doses for pregnant women), regardless of the confirmed presence of infection. Intermittent preventive treatment has been recommended for pregnant women in areas of high transmission [37]. The antimalarial sulfadoxine-pyrimethamine has been found to reduce the burden of malaria in this population [42; 43].

Indoor Residual Spraying

Indoor residual spraying involves the application of long-acting chemicals to the walls and other surfaces of a house. The goals of indoor residual spraying are to reduce both the population density and the life span of infecting mosquitoes. Indoor residual spraying was part of a global eradication effort conducted from 1955 to 1969, which was successful in Europe, the Soviet Republic, parts of Asia, and the Caribbean. The effort did not include the African continent [44].

VACCINES

For years, research has focused on the development of an effective vaccine to prevent malaria in endemic areas [16; 48; 49; 50; 51; 56; 57]. In 2021, the first vaccine to prevent malaria, RTS,S/AS01 (RTS,S), was approved and recommended by the WHO for children in sub-Saharan Africa and in other regions with moderate-to-high malaria transmission [61]. The vaccine is provided in a schedule of 4 doses in children from 5 months of age [62]. More than 2 million doses of the vaccine were administered prior to the WHO's recommendation, with good safety and efficacy [62]. In 2023, a second malaria vaccine, R21/Matrix-M, was approved by the WHO [65]. A phase 1/2b clinical trial demonstrated an 80% efficacy in the high-dose group, with efficacy up to 78% against multiple episodes of malaria disease at two-year follow-up [64]. The vaccine is given in a primary three-dose regimen, with a booster at one year and is the first vaccine to achieve the WHO goal of 75% efficacy. As a more effective and less expensive option, this vaccine is preferred over RTS,S/AS01 (RTS,S) as the vaccine of choice in areas with significant sustained malaria transmission [65]. Along with continued infection prevention strategies, vaccines are expected to drastically reduce the burden of malaria in effected areas. Research continues into additional vaccines, including those that may be appropriate in adults or for travelers.

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

Because patient education is such a vital aspect of preventing the spread of malaria, 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.

CONCLUSION

Malaria is one of the most significant infectious diseases in the world. It affects between 150 and 300 million people each year worldwide and is a leading cause of illness and death in the developing world. Malaria imposes significant costs to individuals and governments. Such costs can add substantially to the economic burden of malaria on endemic countries and impede their economic growth [2; 18].

Malaria poses a particularly serious threat to U.S. travelers who lack immunity. Although the transmission of malaria was successfully interrupted in the United States during the late 1940s, it continues to pose a challenging health threat to individuals who travel to and emigrate from malarious areas. Because malaria cases are rare in the United States, misdiagnosis is a common problem [4; 5]. Malaria may be suspected based on the patient's symptoms, travel history, and physical findings at examination. Patients with suspected infection should be urgently and thoroughly evaluated. Delayed diagnosis is a leading cause of death among malaria patients in the United States [3].

Patients suspected of having malaria infection should be urgently evaluated, and the diagnosis should be confirmed by laboratory investigations before treatment begins. Presumptive treatment, without the benefit of laboratory confirmation, should be reserved for extreme circumstances [4; 5].

RESOURCES

CDC Malaria Hotline
855-856-4713 (Monday through Friday, 9 a.m. to 5 p.m., Eastern)
770-488-7100 (for emergency consultation after hours and holidays)

CDC Travelers' Health
This site contains general traveler's health precautions and malaria-specific information.
The current *CDC Health Information for International Travel* (the Yellow Book) may also be viewed.
https://wwwnc.cdc.gov/travel

The Global Partnership to End Malaria
https://endmalaria.org
The RBM Partnership
Secretariat hosted at WHO
20 Avenue Appia
1211 Geneva 27
Switzerland

CDC Malaria
Guidelines for Treatment of Malaria in the United States
https://www.cdc.gov/malaria/diagnosis_treatment/treatment.html

Malaria Vaccine Initiative
This site contains information about the research into and development of a vaccine for malaria.
https://www.malariavaccine.org

U.S. Food and Drug Administration: Counterfeit Medicine
The site contains information for consumers about counterfeit medications.
https://www.fda.gov/drugs/buying-using-medicine-safely/counterfeit-medicine

COURSE TEST - #94364 MALARIA AND THE INTERNATIONAL TRAVELER

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

This 3 Hour activity must be completed by September 30, 2025.

1. The symptoms of malaria were first described
- A) *by Hippocrates.*
- B) *in ancient Greece.*
- C) *in ancient Chinese medical writings.*
- D) *by indigenous tribes in South America.*

2. How many species of malaria parasites are known to infect humans?
- A) *2*
- B) *5*
- C) *6*
- D) *8*

3. Which of the following factors primarily influence where malaria is found?
- A) *Rainfall*
- B) *Humidity*
- C) *Temperature*
- D) *All of the above*

4. Following an infectious mosquito bite, the symptoms of malaria generally appear after an incubation period of
- A) *7 to 30 days.*
- B) *10 to 15 days.*
- C) *15 to 18 days.*
- D) *18 to 21 days.*

5. Common symptoms of uncomplicated malaria include all of the following, EXCEPT:
- A) *Nausea and vomiting*
- B) *Fever, chills, and sweats*
- C) *Cardiovascular collapse and shock*
- D) *Headache, body ache, and general malaise*

6. The manifestations of severe malaria include
- A) *hyperglycemia.*
- B) *acute liver failure.*
- C) *parasitemia less than 1%.*
- D) *pulmonary edema or acute respiratory distress syndrome.*

7. Which of the following diagnostic techniques is the criterion standard for laboratory confirmation of malaria?
- A) *Serology tests*
- B) *Drug resistance tests*
- C) *Rapid diagnostic tests*
- D) *Giemsa-stained blood smears*

8. The first-line treatment for *P. malariae* malaria is
- A) *chloroquine.*
- B) *hydroxychloroquine.*
- C) *atovaquone/proguanil.*
- D) *Any of the above*

9. Which of the following personal protective measures has been recommended by the CDC for individuals traveling outside the United States?
- A) *Use bed nets (preferably treated) and insecticides.*
- B) *Avoid travel to known malaria-endemic areas, when possible.*
- C) *Be aware of peak exposure times and places and wear clothing that minimizes skin exposure.*
- D) *All of the above*

10. Travelers to malaria-endemic areas should be advised to take a presumptive self-treatment course of antimalarials if they
- A) *discover an insect bite.*
- B) *have immediate access to medical care.*
- C) *have contact with a suspected malaria patient.*
- D) *develop fever, chills, or other influenza-like illness.*

Contraception

This course meets the California requirement for emergency contraception education for those who furnish these medications.

Audience
This course is designed for gynecologists, primary care physicians, nurse practitioners, and other primary care health providers, such as pharmacists, physician assistants, and nurses, who care for women of childbearing age.

Course Objective
Newer contraceptive methods and new techniques for old methods (such as hysteroscopic sterilization) are attractive to patients, and their contraceptive provider (or referring provider) should have a grasp of the wide range of options. The purpose of this course is to provide healthcare professionals with the information necessary to advise patients and prescribe effective and appropriate contraceptives.

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

1. Compare the efficacy rates of different contraceptive methods.
2. Evaluate various barrier and spermicidal contraceptive options.
3. Analyze the action and side effects of different combination oral contraceptive pills.
4. Discuss the risks of long-term progestin-only contraceptive methods.
5. Outline the side effects and alternative indications for intrauterine devices.
6. Compare and contrast traditional (surgical) and hysteroscopic sterilization.
7. Identify special concerns in postpartum contraception.
8. Describe different methods of providing emergency contraception.

Faculty
Julie Quinn, MD, is a board-certified obstetrician-gynecologist who practiced general Obstetrics and Gynecology for four years before transitioning to a career in medical communications. Dr. Quinn completed her undergraduate education at the University of California, Davis, and her medical education at Pennsylvania State University College of Medicine. She completed her training at the Phoenix Integrated Residency in Obstetrics and Gynecology in Phoenix, Arizona.

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

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

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EVIDENCE-BASED PRACTICE RECOMMENDATION

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

INTRODUCTION

Contraception is a topic with which any provider seeing women in a primary care environment should be familiar. It can be challenging to stay up to date with all possible methods and to answer patients' questions about side effects and health risks. It is worthwhile, however, as helping women take control over their reproductive potential is arguably one of the most important jobs in medicine.

Adolescents represent a particular challenge in providing contraception. Although the teen birth rate has declined over the last 20 years and contraceptive use has increased, there remain ethnic and racial differences in the use of highly effective contraception. The teen birth rate in the United States is higher than that of most other developed countries [1; 2; 58]. Half of teen births occur in women who were not using any contraception at the time of conception, and four in five teen pregnancies are unintended [3; 4; 5]. Healthcare providers should have accurate, evidence-based information to provide to all patients, particularly adolescents. Information on highly effective, long-term contraceptive methods can help reduce the ethnic and racial disparity in the use of these methods. An understanding of how teens think about sex and birth control is also crucial, although beyond the scope of this educational activity [6].

The wide range of contraceptive methods and various delivery systems within methods presents a challenge for providers. New formulations are coming out constantly, fueled partly by patient demand for lower hormone doses and fewer side effects. As generics and shorter patents impact the bottom line of pharmaceutical companies, new birth control formulations and delivery systems abound [7].

BACKGROUND AND BRIEF HISTORY OF CONTRACEPTION

According to the Guttmacher Institute, an estimated 46 million women 15 to 49 years of age in the United States are sexually active but not trying to become pregnant [8]. Women are potentially at risk for pregnancy for about 39 years—almost half of their lives. Forty-five percent of pregnancies in the United States are unintended (i.e., 1 in 20 reproductive age women have an unintended pregnancy each year), with almost half of those ending in elective abortion [69]. Unintended pregnancy rates are lower in women with higher education level attainment and higher socioeconomic status. More than half of unintended pregnancies occur in women "using" contraception, but a method will obviously be less effective if not used consistently or properly or if it is not a good contraceptive choice for that patient [4; 8; 9; 69]. More than 99% of sexually active women between 15 and 44 years of age use at least one form of contraception [8; 59; 60].

Contraception is likely as old as pregnancy itself. Before dedicated methods were developed, withdrawal, induced abortion, and even infanticide were practiced. Condoms made from animal bladders or intestines date back to 3000 B.C.E. [10]. Pessaries of honey, crocodile dung, and sodium carbonate were used in Egypt as far back as 1850 B.C.E. Around 600 B.C.E., a fennel-like plant was purported to be an oral contraceptive; unfortunately, this plant was harvested to extinction by 100 C.E. [11]. In the 1500s, when men used linen sheaths to protect against syphilis, crude spermicides were first attempted [4; 10]. Animal intestine condoms were common in the 18th century, with rubber condoms becoming available in the 19th century [4; 10]. Rubber cervical caps and diaphragms have been in use since the early 1900s in Europe [4]. When combination oral contraceptive pills were introduced in the 1960s, the doses of both estrogen and progesterone were much higher than they are today. Gradually, the doses came down as the formulations were improved and refined.

Long-acting methods of contraception (both reversible and permanent) are the most effective. Sterilization, intrauterine devices (IUDs), and progesterone implants are superior to barrier methods and combined hormonal methods, largely because they eliminate user error [12]. Although induced abortion can be used as a method of contraception, the scope of this topic is beyond the range of this educational activity.

Many factors will influence the choice of contraceptive method. The cost-effectiveness of a particular method will come into consideration for most patients. In addition, many hormonal contraceptives also have non-contraceptive benefits and are often used for these reasons [4]. This course focuses, however, on the contraceptive uses of each method, with a brief description of non-contraceptive benefits. It is not the intention to review all possible indications for each method discussed herein. An overview of the effectiveness of each method, expressed as first-year failure rates, is provided as well.

BEHAVIOR-BASED METHODS

First, a note on abstinence. Primary or secondary abstinence is fairly common for contraceptive or other reasons. Patients who practice abstinence should still be educated about contraceptive options, any pertinent non-contraceptive benefits, and methods of preventing sexually transmitted infections (STIs) [4].

Behavior-based birth control methods, also referred to as natural family planning, such as "rhythm" and withdrawal, have limited efficacy. However, they are preferable for many patients, particularly those who do not wish to take hormones or who have religious convictions prohibiting the use of other contraceptive methods.

NATURAL FAMILY PLANNING/FERTILITY AWARENESS-BASED METHODS

Fertility awareness methods depend on identifying the fertile days in each menstrual cycle and avoiding intercourse on those days. Natural family planning advises abstention on fertile days, while fertility awareness-combined methods allow for the use of barrier methods on those days [4]. Of course, these methods may also be used to calculate the likely fertile days in couples trying for conception.

Standard Days/Calendar Methods

The "fertile window" comprises the five days before ovulation, and the day of ovulation itself. In normal 26- to 32-day cycles, the fertile window will fall between cycle days 8 to 19. Using the standard days method, couples avoid intercourse on cycle days 8 through 19. The calendar rhythm method differs slightly, with the woman keeping a record of the length of her last 6 to 12 cycles and calculating the likely fertile days in the current cycle. Briefly, 18 days are subtracted from the length of the shortest cycle to find the first fertile day in the current cycle. To find the last fertile day, 11 days are subtracted from the length of the longest cycle. This method must be updated every month [4]. Women with irregular or short (fewer than 25 days) cycles will not have a high effectiveness with either of these methods [6]. Women in the first few years after menarche and the few years before menopause are prone to irregular cycles, and women who have recently given birth or who are breastfeeding will also have difficulty with these methods [4].

Ovulation Method

The ovulation method uses changes in cervical secretions to identify the beginning and end of the fertile window. Clear, stretchy, slippery secretions indicate fertility; thick, sticky, cloudy secretions determine the end of the fertile window [4]. Abstinence must be enforced from the first day of thin, slippery mucus until four days after resumption of normal cervical secretions [6].

Symptothermal Method

The symptothermal method observes changes in basal body temperature. A temperature rise of at least 0.4 degrees F sustained for three days indicates that ovulation has occurred [4]. Basal body temperature may be taken orally, rectally, or vaginally, in the morning (after awakening but before arising), but the method must be consistent [4; 6]. Abstinence occurs from the first day of the menstrual period until three days of consecutive elevated basal body temperature [6].

The main behavior-based, fertility-awareness methods are, naturally, entirely user-dependent. First-year failure rates are around 20% for the ovulation and symptothermal methods, with the standard days and calendar rhythm methods showing slightly lower failure rates of 12% to 13% [4]. Some sources give failure rates as high as 35.3% (***Table 1***) [8; 59]. None of these methods protect against STIs [4].

Combination Contraceptive Mobile Medical Application

In 2018, the U.S. Food and Drug Administration (FDA) approved marketing of the first direct-to-consumer mobile medical application (app) for contraception. The app, Natural Cycles, uses an algorithm to calculate fertility based on self-reported temperature using a basal body thermometer first thing in the morning and menstrual cycle information. The app is intended for users 18 years of age and older and relies heavily on user consistency. The typical failure rate in one study was 6.5%, which also accounted for women not using the app correctly and/or having unprotected intercourse on decidedly fertile days. While more information is needed on the efficacy of this method, it is the first technologic app to be used as a contraceptive and may lead to further technology-driven methods [68].

WITHDRAWAL

As of 2015, 64.8% of women (including 59.7% of women 15 to 19 years of age) had used withdrawal as a form of contraception at some point [8; 58]. However, only 3.2% used it as a primary method [14; 59]. It is a more common method among adults than adolescents. In this method, also known as coitus interruptus, the penis is withdrawn from the vagina and moved away from the external genitalia prior to ejaculation. This relies on the male's sensation that ejaculation is imminent. With perfect use, the rate of pregnancy in the initial year of use should be about 4%; with typical use, a 20% failure rate is seen [4; 8].

ANNUAL CONTRACEPTIVE FAILURE RATES		
Contraceptive	**Failure Rate with Perfect Use**	**Failure Rate with Typical Use**
No method	N/A	85%
Fertility awareness methods (includes periodic abstinence, ovulation method, and symptothermal method)	0.4%–5%	28%
Withdrawal	4%	20%
Spermicide	18%	28%
Male condom	2%	13%
Female condom	5%	21%
Diaphragm	6%	12%
Sponge (parous/nulliparous)	20%/9%	24%/12%
Cervical cap (parous/nulliparous)	26%/9%	40%/20%
Combined oral contraceptive pills (COCs)	0.3%	8.7%
Transdermal patch	0.3%	9%
Vaginal ring	0.3%	9%
Progestin-only pills (POPs)	0.3%	13%
Depot medroxyprogesterone acetate (DMPA) injection	0.2%	4%
Progestin implant	0.05%	0.05%
Levonorgestrel intrauterine device (IUD)	0.2%	0.2%
Copper-T IUD	0.6%	0.8%
Female sterilization	0.5%	0.5%
Male sterilization	0.1%	0.15%
Source: [4; 8; 13]		*Table 1*

The advantages of this method include its price (free) and its nonhormonal nature. It does not involve calculating cycle times, as natural family planning methods do. The disadvantages include the failure rate, its extreme user-dependency, and the fact that it does not provide adequate protection from STIs. Pre-ejaculate may contain pathogens, and skin lesions are not protected [4].

BARRIER AND SPERMICIDAL METHODS

Many patients who do not wish to use a hormonal form of contraception find barrier and spermicidal methods preferable. In addition, condoms (male and female) remain the only method of birth control that reliably protects against most STIs.

Any barrier or spermicidal method has the potential to cause discomfort or irritation and may predispose to bacterial vaginosis or urinary tract infection. There is also a small risk of toxic shock syndrome with female barrier methods such as the diaphragm and cervical cap. Latex allergies must also be taken into account with male condoms [4].

VAGINAL SPERMICIDES

Vaginal spermicides can be used alone or with barrier methods of contraception. They come in the form of gels, foams, creams, films, suppositories, or tablets. Products in the United States contain nonoxynol-9, a surfactant that destroys sperm cell membranes. Films, suppositories, and tablets must be given adequate time to dissolve against the cervix before intercourse. The products must also be left in place for at least six hours after intercourse [4]. Vaginal spermicide methods are inexpensive but do not have a high efficacy with typical use (***Table 1***).

MALE CONDOMS

Male condoms are widely available, inexpensive, and popular. An estimated 95% of women have used this form of contraception at some point [14; 60]. Among women currently using contraception, an estimated 8% to 13% use condoms as part of their repertoire [4; 8; 59; 70]. Condoms are much more frequently used by adolescents (approximately 56% of unmarried teenage women report using a condom at last intercourse), and condom use among adolescents continues to increase [58].

The male condom provides good protection against bacterial and viral STIs. It acts as a physical barrier and is most effective when worn for the entire act of intercourse, with a fresh condom used for repeated acts. Latex or polyurethane condoms are most effective for STI protection, although "natural" condoms (lamb cecum) are also available for contraception [9]. Latex and synthetic condoms can also be used during oral or anal intercourse to prevent STIs [4].

Latex condoms must not be used with oil-based lubricants; natural or polyurethane condoms do not have this restriction. Condoms often come with, or are used with, the spermicide nonoxynol-9, although this has not been proven to increase contraceptive efficacy and may cause adverse effects such as genital ulceration, irritation, or urinary tract infections [4].

FEMALE CONDOMS

The female condom also provides good protection against bacterial and viral STIs [9]. It has been available in the United States since 1993 and acts as a physical barrier that lines the vagina and partially covers the vulva and perineum. It consists of a closed-end ring that is the internal anchor and an external, open ring. Made of polyurethane, it is stronger than latex and is compatible with oil-based lubricants [4]. Female and male condoms should not be used together. Statistics indicate that female condoms are not popular [58; 70].

DIAPHRAGM

The diaphragm is a rubber cup that is placed at the end of the vagina with the posterior rim in the posterior fornix and the anterior rim behind the pubic bone. Spermicide is placed on the inner surface, ensuring its application next to the cervix. Unlike male and female condoms, diaphragms must be fitted by a healthcare practitioner [4]. When used with spermicide, the diaphragm provides some protection against bacterial and viral STIs, but not nearly to the extent that more extensive, skin-covering barrier methods such as condoms provide [9]. The concomitant use of spermicide is recommended, although large-scale studies to prove increased efficacy have not been conducted [4].

Once inserted, the diaphragm is considered effective for six hours. The device must be left in place for six additional hours after intercourse. If it is left in place for longer than six hours total, it is recommended to apply additional spermicide. Due to risk of toxic shock syndrome, use for longer than 24 consecutive hours is not recommended [4].

CERVICAL CAP

The cervical cap is similar in concept to the diaphragm, but much smaller. It is a deeper cup that fits snugly around the base of the cervix. Spermicide is used to fill the inner surface one-third full. The cap may be left in place for 48 hours and does not require additional spermicide for repeated acts of intercourse [4].

SPONGE

The contraceptive sponge provides both contraception and some protection against STIs [15]. It was first approved in the United States in 1983, then taken off the market in 1995 for business reasons. As of 2012, the sponge, under a different manufacturer, is once again available in the United States.

The device consists of a polyurethane sponge containing nonoxynol-9. It is moistened with water and placed in the vagina, with the dimpled surface against the cervix. The outer surface has a ring for removal. The sponge may be worn for 24 hours and must be left in place for 6 hours after intercourse [4].

HORMONAL METHODS

COMBINED ORAL CONTRACEPTIVE PILLS

Combined oral contraceptive pills (COCs), which have been available for more than 50 years, have undergone radical changes and today's pills would be unrecognizable to the original inventors. An estimated 80% of U.S. women born since 1945 report using oral contraceptive pills at some point in their lives [8; 9]. Among women 15 to 49 years of age, oral contraceptives are the most commonly used nonpermanent contraceptive method [8; 59]. New doses and formulations are rapidly being produced, in addition to different delivery vehicles such as the intravaginal ring, and health concerns are frequently raised on existing pills. The wide range of progesterones used in combination oral contraceptive pills affects their side effect profile, and many primary care providers may not be aware of how to adjust oral contraceptives in order to minimize side effects.

COCs are taken daily, and formulations vary regarding how many days involve hormone pills. The traditional regimen involves 21 days of hormones, followed by 7 days of placebo pills to allow for a withdrawal bleed. Many newer formulations have 24 days of hormones, with a shortened placebo period to adhere to a 28-day cycle [15]. Still others administer continuous hormones for 84 days or longer [12; 15]. Women on continuous COCs experience more breakthrough bleeding, but women on these longer regimens experience reduced follicular development and reduced symptoms during the hormone-free period [11; 15].

Pills may be started on the Sunday following the onset of menses (referred to as the traditional "Sunday start"), or by "quick start" at any time of the cycle. Quick start has been shown to increase compliance and has the same incidence of abnormal bleeding as a Sunday start. Depending on the timing, backup contraception may be needed for the first seven days. If the quick start occurs in the first six days of the cycle, no backup is needed; if it occurs in the last 14 days of the cycle, backup contraception and a pregnancy test are needed as conception may already have occurred [12].

Mechanism of Action

The estrogen component of COCs inhibits follicle-stimulating hormone (FSH) and endometrial proliferation, providing cycle control. The progesterone component provides the main contraceptive effect, inhibiting the luteinizing hormone (LH) surge that triggers ovulation and thinning of the endometrium; it also thickens cervical mucus, which inhibits sperm motility and function [9; 12]. Combined, they suppress ovulation and produce a thin, asynchronous endometrium with decreased tubal mobility [12]. Almost all COCs in the United States use ethinyl estradiol for their estrogen component, although a newer estradiol-based contraceptive, Natazia (estradiol valerate and dienogest), was approved by the FDA in 2010 [9; 16; 18].

Estrogen Side Effects

The lower the dose of estrogen, the fewer the side effects, including nausea, headache, and breast tenderness, as well as more serious side effects such as the risk for venous thromboembolism (VTE). When the estrogen dose is lowered, however, the risk for other side effects rises. Breakthrough bleeding and spotting is much more common in lower-estrogen pills [9].

Progestin Side Effects

There are many different types of progesterone used in COCs, and their androgenic effects have a wide range. The three progestins that have the lowest androgenic side-effect profile are norgestimate, desogestrel, and drospirenone. Progestins with higher androgenicity may increase acne and may antagonize estrogen's beneficial lipid profile to a greater degree. For patients experiencing these side effects or for patients who have acne or hyperlipidemia to begin with, a less androgenic progestin is indicated. Desogestrel and drospirenone, however, seem to have a higher risk of VTE compared with levonorgestrel, a more androgenic progestin [9; 17]. Drospirenone is a derivative of spironolactone and has antimineralocorticoid effects. It is beneficial for acne and has an indication for premenstrual dysphoric disorder (PMDD), but it must not be used with spironolactone or daily nonsteroidal anti-inflammatory medications, or for patients with renal, adrenal, or hepatic compromise. It is recommended to check serum potassium in any woman on drospirenone and a second medication that may affect potassium levels (e.g., heparin, angiotensin converting enzyme inhibitors, diuretics) [18].

Continuous Dosage

Continuous dosage, whereby a woman takes COCs for 3, 6, or 12 months before taking a placebo week, is useful for women with severe dysmenorrhea, PMDD, or breakthrough bleeding on lower dose regimens. If an extended regimen does not eliminate breakthrough bleeding after three months, the estrogen dose should be raised or a different method found if the patient is already on a 35-mcg pill [9]. Most extended regimens, however, use lower doses of estrogen [15].

Non-Contraceptive Benefits

Oral contraceptive pills have benefits other than contraception. They are often used for control of menorrhagia and/or dysmenorrhea and have been shown to have beneficial effects in women with leiomyoma [71]. They promote cycle regularity, decrease blood loss from menstrual periods, and decrease both dysmenorrhea and iron-deficiency anemia. Like all contraceptives, they decrease the risk for ectopic pregnancy by reducing pregnancy risk itself. COC users have fewer instances of ovarian cysts and decreased fibroadenomas and fibrocystic breast changes. Newer, lower-estrogen pills may not have the benefit of reducing functional ovarian cysts; patients with this concern may need higher-estrogen pills. COCs are useful for the treatment of endometriosis and perimenopausal symptoms in younger women as well. They may also have beneficial effects on bone mass and rheumatoid arthritis. Finally, COCs decrease the risk of pelvic inflammatory disease (PID) by thickening cervical mucus, impeding the ascent of pathogens [9; 20; 21].

Risks/Contraindications

Unless otherwise stated, the risks of COCs apply to other combined methods of contraception, such as the transdermal patch and vaginal ring, as well. The American College of Obstetricians and Gynecologists (ACOG) states that progestin-only or non-hormonal methods may be safer for women with the following: history or risk of VTE or inherited thrombogenic mutations; history of migraines with neurologic symptoms (aura); smoking after age 35 years; hypertension; systemic lupus erythematosus (SLE) with positive (or unknown) antiphospholipid antibodies [19]. COCs should not be used in women who have had diabetes for more than 20 years and/or have evidence of microvascular disease and in women who have breast cancer. Women who are postpartum fewer than three weeks should also use non-estrogen-containing contraception [19].

Venous Thromboembolism

The estrogen component of birth control pills does increase the risk for VTE, as it increases hepatic production of factors involved in coagulation [19]. The clot risk for most modern pills (less than 50 mcg ethinyl estradiol) is about three to four times that of women not on hormonal contraception, although it remains much lower than the clot risk during pregnancy, which is 12 times that of women not on hormonal contraception [4; 12; 19]. Pills containing desogestrel as their progesterone component pose a clot risk similar to those with levonorgestrel [19]. Drospirenone has also received publicity about a possible increased clot risk compared with other progesterones. An FDA review had cautioned that it was possibly associated with a higher risk of blood clots, but the data were not conclusive [17]. It is now thought that the risk of clots with drospirenone is similar to that of older formulations of progesterone [19].

Women who have had a previous unexplained blood clot or one associated with pregnancy or estrogen use are not candidates for COC use, regardless of progesterone type. If a woman is currently on anticoagulant therapy or had a non-recurring risk factor for the clot, then COC use may be considered

[19]. Oral contraceptive pills do not increase VTE risk for appropriately anticoagulated patients [12; 19]. Women on anticoagulation therapy may also consider the depot progesterone injection to suppress ovulation and therefore prevent bleeding from the corpus luteum. The levonorgestrel IUD will decrease menorrhagia from anticoagulation but often will not prevent ovulation [19]. The use of estrogen-containing emergency contraception has not been shown to raise the risk for VTE [22].

Other risk factors for VTE include increasing age, obesity, surgery, air travel, postpartum status, and coagulation disorders [19]. These risk factors should be considered when prescribing COCs. The Centers for Disease Control and Prevention (CDC) recommends that postpartum women should not use COCs during the first 21 days after delivery due to a high risk for VTE during this period [23]. The coagulation disorders most likely to predispose to clot while on COCs are Factor V Leiden, prothrombin gene mutation, Protein C, Protein S, and antithrombin deficiency. Women heterozygous for Factor V Leiden have a clot risk 6 to 8 times that of healthy young women; this risk rises to 10 to 15 times when Factor V Leiden patients take COCs [12]. Even so, the ACOG does not recommend screening for these disorders in women who have never had a clot, as the likelihood of experiencing a de novo clot, even on COCs, is extremely low [19]. However, if a first-degree relative has a known thrombophilia or unexplained VTE, screening is recommended [12; 19]. If a patient is already known to have a clotting disorder, a different contraceptive method should be sought [19]. In general, it is advisable to stop estrogen-containing contraceptives one month before major surgery or arthroscopic surgery, as prolonged immobilization raises the risk for VTE. This must, of course, be balanced against the risks involved in unintended pregnancy. Heparin prophylaxis may be used if oral contraceptives are not stopped before surgery. COCs may be continued before laparoscopic tubal ligation or other minor procedures that do not raise VTE risk through [19].

Cardiovascular Events

The risk of thrombotic stroke and myocardial infarction is also increased in women on estrogen-containing contraceptives. Although these risks remain low in terms of absolute risk, the relative risk is higher with higher oral doses of estrogen (i.e., ≥50 mcg) and with the patch and ring delivery systems [24]. Smoking, hypertension, and diabetes all increase the risk for cardiovascular disease, although they do not directly increase clot risk [19; 25]. In women with hypertension taking COCs, the relative risk of acute myocardial infarction increases by a factor of twelve compared with those women not using COCs; despite this, the absolute risk of myocardial infarction remains low. Non-contraceptive benefits of COCs should also be considered in these patients when making the decision to prescribe oral contraceptives. Non-estrogen-containing methods may be preferred.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Centers for Disease Control and Prevention, the risk for cardiovascular disease increases with age and might increase with combined hormonal contraception use. In the absence of other adverse clinical conditions, combined hormonal contraception can be used until menopause.

(https://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6503.pdf. Last accessed June 15, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

The risk for stroke in reproductive-age women is low, but the risk factors may be synergistic and include smoking, age older than 35 years, obesity, family history of early stroke, hypertension, diabetes, hyperlipidemia, and migraine (both with and without aura) [9; 26]. Healthy women not on COCs have half the absolute stroke risk of those on COCs; with migraine, the risks go up to double (no COCs). Migraine with aura raises the risk even further (up to 12 times greater odds) [19]. COCs may be used in women with migraines without aura (focal neurologic signs) [19]. If a woman has any type of migraine and is older than 35 years of age, it is generally advisable to find a different form of contraception. Before the age of 35 years, COCs may be given to non-aura migraine sufferers after weighing the risks and benefits. Women experiencing auras should not be prescribed COCs [9; 19; 26]. Clinicians may consider giving lower-estrogen pills or continuous pills for women whose headaches are triggered by the withdrawal of estrogen. These women will require close follow-up in the first few months on oral contraceptives [9].

Due to the risks described for stroke and myocardial infarction, women older than 35 years of age who smoke and/or have multiple other risk factors should not use COCs. It is generally considered advisable to use non-estrogen contraceptives in these women [9; 19; 26]. Non-smokers older than 35 years of age may continue to use COCs, individualizing care and exercising caution in patients with obesity or other cardiovascular risk factors.

Perimenopausal women may enjoy the beneficial effects on bone density and vasomotor symptom reduction, but the possibility of breast cancer risk should be weighed against these benefits. As there are limited data on COCs and breast cancer risk in perimenopausal women, the risk is considered to be similar to that of women on hormone replacement therapy. Progesterone-only and non-hormonal methods (such as the copper IUD) may be used in patients concerned about this risk. However, COCs seem to confer a decreased risk for endometrial and ovarian malignancies [19; 21].

Cancers

COCs are thought to reduce the risk for ovarian and endometrial cancer, and this risk reduction persists for many years after stopping use [21]. The effect on breast cancer risk has been controversial, but the vast majority of studies indicate that current or former COC use is not associated with an increased breast cancer risk in reproductive age women (contrasted with perimenopausal women, as discussed) regardless of the estrogen dose, duration of use, or family history of breast cancer. There also appears to be a small reduction in the risk for colorectal cancer, along with a possible increased risk of cervical cancer. It is not known whether the cervical cancer risk is due to the pills themselves or the fact that women on COCs are less likely to use barrier methods to protect themselves from human papillomavirus infection [9]. COCs may be used in women with benign breast disease or even a family history of breast cancer with *BRCA1* or *BRCA2* mutations [27; 28]. As these mutations increase the risk for ovarian cancer, the effect of COCs to decrease this risk is an important benefit [19]. They are, however, contraindicated in patients with current or past breast cancer [9; 12].

Obesity

Obesity raises the risk for COC failure and patch failure by altering how the drugs are absorbed, distributed, metabolized, or eliminated [29; 30]. In women with obesity, steady state contraceptive steroid levels take longer to achieve when initiating therapy and after the hormone-free period [19]. ACOG suggests that a continuous oral contraceptive or a higher dose therapy may be more effective in this cohort if an oral therapy is desired by the patient.

Obesity also raises the clot risk above that conferred by the contraceptive method itself. One study showed a 10-fold higher clot risk in women on oral contraceptives with a body mass index greater than 25, compared with leaner women. However, if overweight or obese women are more likely to use these methods than those with higher failure rates (e.g., behavior-based methods, barrier methods), the risks must be weighed against the risks of unintended pregnancy. A thorough discussion on contraceptive methods, including progesterone-only methods and intrauterine devices (neither of which seem to be affected by body weight), is appropriate for any overweight or obese patient [19; 23]. Indeed, a thorough discussion on all available contraceptive methods is appropriate for any patient desiring contraception.

Hypertension

Women with hypertension must have their care individualized. COCs may increase blood pressure and do increase the risk for myocardial infarction or stroke, although the absolute risk remains low. These risks must be weighed against the risk of a pregnancy complicated by hypertension, as well as against the non-contraceptive benefits of COCs. ACOG and the CDC have identified increased risks associated with COCs when blood pressure is systolic 140–159 mm Hg or diastolic 90–99 mm Hg [19]. In patients with systolic 160 mm Hg or greater or diastolic 100 mg Hg or greater, or in patients with vascular disease, COCs are absolutely contraindicated [19]. Progesterone-only and non-hormonal methods may be used in these patients [19; 23]. In women younger than 35 years of age with well-controlled hypertension without other risk factors, a well-monitored trial of COCs may be undertaken [9; 19].

Diabetes

COCs may be used in women with uncomplicated diabetes, and they do not appear to precipitate development of type 2 diabetes in women at risk for the condition [19; 23]. If there are any other heart disease risk factors in a patient with diabetes, however, COCs are contraindicated. When choosing a COC for a patient with diabetes, keep in mind to choose a pill with a low estrogen dose (as estrogen decreases insulin release) and a progesterone with low activity (as progesterone is a competitive inhibitor of insulin) [9]. Low-progesterone agents include norgestimate, norethynodrel, norethindrone, and ethynodiol [31]. COCs are not contraindicated in women with a history of gestational diabetes that resolved in the postpartum period [9]. As discussed, COCs should not be used in women who have had diabetes for more than 20 years and/or who have evidence of microvascular disease [19].

Systemic Lupus Erythematosus (SLE)

Women with mild, stable SLE, with no history of antiphospholipid antibodies, vascular disease, or nephritis, may safely use COCs, although many practitioners steer these patients toward IUDs [19]. If antiphospholipid antibody status is unknown, this should be ascertained before initiating hormonal contraception. COCs are contraindicated in women with SLE and positive antiphospholipid antibodies [19].

Depression

COCs are not thought to have an effect on depression or on the efficacy of commonly prescribed antidepressants. St John's wort is a hepatic enzyme inducer and increases the risk of ovulation in women on COCs [19; 23]. If this supplement is being used, a backup or alternate birth control method should be considered.

Drug Interactions

Some anticonvulsants may induce hepatic enzymes and decrease levels of COC steroids. It has not been proven whether increasing pill dosage overcomes this effect; therefore, the use of backup condoms or switching to an IUD should be considered in women on these medications, including barbiturates, carbamazepine, oxcarbazepine, phenytoin, primidone, felbamate, topiramate, vigabatrin, and lamotrigine [12; 19; 23]. Depot progesterone injection increases the seizure threshold and therefore is a good contraceptive choice for these patients [12].

The clinical impact of antiretroviral medications on COC users is unknown [19]. Theoretically, any antiretroviral that induces cytochrome P450, including fosamprenavir, may decrease COC effectiveness and a backup method would be indicated [12; 23]. In addition, there is evidence of an increased risk of

acquiring HIV among progestin-only injectable users; however, there are no firm data to determine whether COCs affect HIV transmission. The CDC recommends that women considering progestin-only injectables should not be denied use but should be advised that there is uncertainty over whether there is a causal relationship [61].

Despite much anecdotal "knowledge" to the contrary, rifampin/rifabutin and griseofulvin are the only antibiotics known to decrease steroid hormone levels in COC users. Backup contraception should be used when taking rifampin or griseofulvin, but this is not necessary for other antibiotics [12; 18; 19].

Other Conditions

According to the World Health Organization (WHO), there are no restrictions for COC use in women with mild, compensated cirrhosis, chronic viral hepatitis, or carriers of the hepatitis virus. In women with acute hepatitis, the risks usually outweigh the benefits for initiating use of COCs. However, COC use is contraindicated in women with severe liver disease [23; 32]. Symptomatic gallbladder disease is also a relative contraindication [9]. Undiagnosed genital tract bleeding is a contraindication to COC use [12]. Pregnancy should always be ruled out if bleeding occurs while on a hormonal contraceptive.

CONTRACEPTIVE PATCH

As of 2024, there were two types of contraceptive patches on the market. The first contraceptive patch delivers both estrogen (35 mcg/day ethinyl estradiol) and progesterone (150 mcg/day norelgestromin), and the second contraceptive patch delivers 30 mcg/day ethinyl estradiol and 120 mcg/day levonorgestrel [18]. The contraceptive patch operates on the same mechanism of action as COCs: gonadotropins are suppressed, the cervical mucus is thickened, and endometrial changes occur [9; 15; 33]. The patch is changed once weekly for three weeks of hormone dosage, then one week is allowed patch-free for withdrawal bleeding to occur [18; 33]. There is a two-day "patch forgiveness" window to change patches without losing efficacy [9].

Each patch is considered to have similar risks and benefits to their equivalent formulation COCs, except as described in the following sections. Possible side effects include breast discomfort, headache, nausea, skin reaction at the application site, dysmenorrhea, acne, hair loss, and abdominal pain [9; 18; 33].

The contraceptive patch has beneficial effects on lipid levels, increasing HDL and decreasing LDL [19]. Similar to oral contraceptive pills, the patch has a higher failure rate for heavier women, particularly those weighing more than 90 kg (198 lbs) [9; 18]. Both patches are approved for women with a BMI <30 [18].

The same contraindications apply for the patch as those described for COCs. There is an increased thromboembolic risk with this method, as there is with COC use, and the same cautions should be used in patients with risk factors for VTE or cardiovascular disease [18]. The contraceptive patch results in higher estrogen exposure for patients—60% higher than women on 35 mcg COCs—and there is a higher risk for developing VTE compared with women on COCs [12; 18]. The relative risk for VTE for women on contraceptive patches, compared with women on COCs, has been reported to be 2.3 [34]. Again, the entire risk/benefit profile must be taken into account, including the risk of VTE in pregnancy, which remains higher than any contraceptive method [12]. Although COCs and the ring may be used continuously, patients should maintain one patch-free week each month because of the higher estrogen dose [12; 18].

VAGINAL RING

There are currently two vaginal rings on the market. The first vaginal ring (NuvaRing) contains ethinyl estradiol (15 mcg/day) and etonogestrel (120 mcg/day), and the second vaginal ring (Annovera) contains ethinyl estradiol (0.013 mg/day) and segesterone acetate (0.15 mg/day) [18]. The mechanism of action is the same as that of COCs and contraceptive patches [35].

The NuvaRing silicone ring is 5.4 cm in diameter and well-tolerated, although it sometimes produces an increased physiologic discharge, headache, weight gain, or nausea [15]. It is disposed of once monthly (three weeks in, one week ring-free for withdrawal bleeding to occur), although it can be left in place continuously for up to 35 days [35]. In 2018, the FDA approved another vaginal ring, Annovera, that may be used for one year, with washing and storage of the ring during the one ring-free week per month [18; 62]. If the ring is removed for more than three hours during the three weeks of dosing, a backup contraceptive is needed for seven days [35]. The ring provides good cycle control and sustained low-dose hormones. The local delivery of hormones avoids the first-pass hepatic effect and the consequent effects on lipids [9].

Although the serum levels of hormones are lower with the vaginal ring than with the patch or COCs, the ring is thought to have a similar clot risk to the patch (i.e., higher than that of COCs) [24; 34]. The relative risk of ring users, compared with COC users, for VTE has been reported to be 1.9 [34]. However, 2012 data seem to show a risk comparable to, not higher than, COCs [36]. More data are required on the annual vaginal ring approved in 2018 to determine the risk of VTE and other adverse effects [62].

Body weight does not appear to have an effect on the ring's efficacy, and vaginal miconazole does not decrease the efficacy of the ring for contraception [12].

PROGESTIN-ONLY PILLS

Progesterone-only contraceptives come in the form of pills, patches, subcutaneous implants, injections, and intrauterine devices. These are used for various indications and patient preferences and have their own health concerns and side effect profiles. Their mechanism of action is the same as that of the progesterone component of COCs: thinning of the endometrium, thickening of cervical mucus, and inhibiting the LH surge that triggers ovulation [12].

Progestin-only pills suppress ovulation, but because there is no estrogen to provide back-up for the progesterone, they are very time sensitive and dependent on patient compliance. Patients must take these pills at the same time every day. If a dose is missed by even three hours, a backup method of contraception is needed [12]. In addition, any concomitant medication that induces liver enzymes (such as antiretrovirals) will lower the already low dose of progesterone in serum and a different contraceptive method should be sought. Progesterone-only pills and implants have lower serum progestin levels than COCs.

Progesterone-only pills make women more prone to irregular bleeding (30% to 40% rate) [12]. They can decrease overall blood loss and dysmenorrhea, and there is no delay in return to fertility once they are discontinued [12]. Breakthrough bleeding on any progestin-only method should be evaluated to rule out pregnancy, infection, or cervical/uterine pathology.

Progesterone-only methods of contraception have the advantage of not raising VTE risk, as estrogen-containing methods do. Therefore, they may be used in many of the medical conditions for which COC use is contraindicated or limited. Progesterone-only pills should not be used in women with current or past breast cancer [9].

Historically, a prescription has been required for access to COC and progestin-only pills. ACOG issued an opinion in 2019 (reaffirmed in 2021) supporting over-the-counter access to hormonal contraception without age restrictions [72]. In the opinion, the authors note that over-the-counter access has continuation rates of hormonal contraception comparable to prescription-only access and has the potential to decrease unintended pregnancy. In 2023, the FDA approved the first daily oral contraceptive for use in the United States without a prescription: a norgestrel tablet (Opill) [73].

Pharmacists furnishing self-administered hormonal contraception should follow established protocols and state laws. In general, patients are asked to complete a self-screening tool, which is then reviewed by the pharmacist. If indicated, the patient's seated blood pressure may be measured and recorded. Patients should also receive education on dosage, effectiveness (including the need to take at the same time every day), potential side effects, safety, the importance of preventive health screenings, and STI prevention [74]. Some states require that the pharmacist refer the patient for appropriate follow-up and notify the patient's primary care provider of the drug being furnished (either directly or via written record provided to the patient) [74].

PROGESTERONE DEPOT INJECTION

The progesterone injection, depot medroxyprogesterone acetate (DMPA), is typically given as a 150-mg intramuscular injection once every three months. The progesterone acts to suppress ovulation by inhibiting the hypothalamic-pituitary-ovarian axis and also thins the endometrial lining [37]. This produces the unwanted side effect of unpredictable bleeding for the first several months but often leads to amenorrhea in the long term [9]. This can be useful in women with menorrhagia from leiomyoma, and DMPA is often used for this purpose. It can be used to temporize, or even prevent, hysterectomy for this indication [19]. DMPA is also often used for the management of endometriosis-related pain. Women on the contraceptive injection experience a decrease in dysmenorrhea, ovarian cysts (better than low-dose pills), endometriosis symptoms, seizures, PID, anemia, and fibroids [9]. The convenience and high efficacy rate (failure rate is 0.2%) of DMPA have made it increasingly popular with adolescents [8; 38].

As noted, frequent spotting is common, particularly after the first injection, but periods typically become very light after the second injection, with many women going on to amenorrhea (50% to 60% at one year) [9; 15]. Breakthrough bleeding on any progestin-only method should be evaluated to rule out pregnancy, infection, or cervical/uterine pathology. Once this is done, generally all that is needed is reassurance that bleeding is common during the first three to six months. COCs may be used for one cycle, or ibuprofen up to 600 mg three times daily may be taken for five days, to decrease bleeding [12]. The injection is an excellent option for women with poor compliance with daily, weekly, or even monthly methods. DMPA does not provide protection from STIs [9]. Upon discontinuing DMPA, there can be a significantly delayed return to fertility of up to 9 or 10 months [12].

There is much anecdotal evidence that the contraceptive injection causes weight gain, but this has not been proven in controlled studies [9]. Weight gain, when it occurs, can be up to 5 pounds at one year of use, and 16 pounds at five years of use. It is thought that the weight gain occurs due to a progesterone-induced increase in appetite, not a decrease in metabolism [12]. This modest increase in body weight does not appear to diminish the effectiveness of DMPA in preventing pregnancy [12; 19].

Women who have migraines with aura while on DMPA, those with current deep vein thrombosis or pulmonary embolism, active liver disease, unexplained vaginal bleeding, or increased cardiovascular risk (e.g., hypertension with vascular disease, diabetes longer than 20 years, history of stroke, ischemic heart disease) are not good candidates for DMPA. Women with hormonally sensitive breast cancer should not use DMPA [9; 23].

Long-term use may slightly improve depressed mood, and depression is not a contraindication [19]. In some women, however, progesterone-only methods may cause an increase in depression. This is a particular problem with the injected form, as it is not possible to "stop using" the contraceptive. It is advisable to use caution in women with a history of severe depression, including postpartum depression. It may be worth a trial of oral progesterone before prescribing the contraceptive injection in women with a history of depression [4].

Women on anticoagulation therapy can also use DMPA to suppress ovulation and prevent bleeding from the corpus luteum [19]. Women with seizure disorders may benefit from DMPA as a contraceptive, as it raises the seizure threshold [4; 12; 19]. Anticonvulsants have no effect on DMPA's effectiveness [4].

DMPA reduces the risk of painful sickle cell crisis by stabilizing red blood cell membranes, making sickle crises fewer and less intense; it can be a good contraceptive choice for women with this disease [12]. There is no evidence that the same precaution regarding antiretroviral use (decreased serum hormonal levels due to liver enzyme induction) applies to this contraceptive, as it does to the progesterone-only pills and implants [19; 23].

The DMPA injection reduces the risk for endometrial hyperplasia and cancer. It is contraindicated in women with current or past breast cancer, and relatively contraindicated in women with a personal history of breast cancer (absolutely if hormone sensitive). It should be used with caution in women with active liver disease or liver tumors [9; 23].

Another side effect that steers many women away from DMPA is the well-publicized loss of bone mineral density while on this medication. The large dose of progesterone suppresses estradiol production from the ovaries, impacting bone mineral density. There have been no cases of osteoporosis or bone fracture while on DMPA, and bone mineral density appears to return to the level of non-DMPA users within 12 to 30 months of discontinuing the medication, with adult former users having similar bone mineral density to those who never used the medication [12; 39]. However, the FDA recommends no more than two years of use unless there is no other acceptable contraceptive method available [40]. The Society for Adolescent Medicine does not restrict use to two years [12]. Likewise, the ACOG does not impose a two-year limit on the use of DMPA, but it does recommend that women, particularly adolescents, exercise and take calcium and vitamin D; the ACOG does not recommend estrogen supplementation [9; 39; 40]. It also notes that implants and IUDs do not impact bone mineral density. The ACOG also notes that the bone loss seen with DMPA is similar to the temporary bone loss seen in pregnancy and breastfeeding (i.e., no long-term loss is observed) [39; 40]. The concern is that adolescents using DMPA are losing bone at a time of their life when they would typically be building bone. The loss of bone mineral density while on DMPA has unknown long-term effects on fracture risk later in life [12]. It is thought that bone density deficit is greater in women who started DMPA before 21 years of age and those who have used it for longer than 15 years [4]. At this time, dual-energy x-ray absorptiometry scanning is not recommended for otherwise healthy women on DMPA [40].

PROGESTERONE IMPLANTABLE DEVICE

The progesterone implant (Norplant) system of six subdermal progestin rods has not been available since 2000 [15]. A single-rod progesterone implant device (Implanon) was approved by the FDA in 2006 and consists of a 4-cm subdermal implant containing etonogestrel, the active metabolite of desogestrel, released at the rate of 60 mcg/day [9; 12]. Nexplanon is the second generation of Implanon. It utilizes a new inserter and contains barium to allow localization with x-ray [41]. The progesterone in this device is released over a three-year period, inhibiting ovulation, altering the endometrial lining, and thickening cervical mucus. It has a low failure rate (***Table 1***), and there is a rapid return to fertility after device removal [12; 37]. It is considered effective eight hours after insertion [12]. Along with both types of intrauterine devices, the progesterone implant is considered a long-acting reversible contraceptive (LARC). LARCs are favorable for their lack of user-dependency and long-term effects [37].

The device can be inserted at any time during the menstrual cycle, after confirming that the patient is not pregnant. A backup method of contraception should be used for seven days, unless the device is inserted within five days of the first day of menses [9; 37]. A backup method is not needed if the device is inserted immediately after childbirth or abortion or if there has been no gap between this method and another hormonal method of contraception [37]. The contraceptive implant may be used postpartum. Although some guidelines advise waiting at least four weeks before insertion, it has not been shown to have any effects on breast milk or infant growth and the ACOG supports the use at any time postpartum [37].

Side effects include irregular bleeding, with prolonged bleeding common (>14 days: 18%); eventual amenorrhea is also common (22% at three months) [18]. Heavier patients tend to experience more bleeding episodes; however, there is no decrease in contraceptive effectiveness in overweight or obese women [37; 42]. Other side effects can include weight gain (in 6% to 14% of users), headaches (25%), and acne (14%) [18; 37]. Although acne usually improves with progesterone-only contraceptives, it can worsen in 10% to 14% of women. Gastrointestinal upset/abdominal pain, breast pain, and vaginitis can also occur. There can be pain and bleeding at the time of insertion or removal. Mild insulin resistance can be a side effect, but with no effect on blood-glucose levels in healthy women. The device is not contraindicated in women with diabetes, as the benefits of the birth control method are thought to outweigh the risks [23; 37]. The progesterone implant does not appear to have an effect on bone mineral density, although data are limited at this point. The relative risk for VTE, compared with that of women not using any hormonal medications, has been reported to be 1.4 [34].

The progesterone insert has no effect on the likelihood of ectopic pregnancy [37]. Breakthrough bleeding on any progestin-only method should be evaluated to rule out pregnancy, infection, or cervical/uterine pathology. Once this is done, reassurance that bleeding is common during the first three to six months may be necessary. COCs may be used for one cycle or ibuprofen up to 600 mg three times daily for five days to decrease bleeding [12]. This method offers no protection against STIs.

INTRAUTERINE DEVICES

IUDs are extremely effective birth control, and they have one of the highest satisfaction and continuation rates among patients [37]. They are available in both hormonal and non-hormonal forms. They are considered LARCs, remarkable for their lack of user-dependence and their rapid return to fertility upon

removal [37]. There are two IUDs currently available in the United States: the levonorgestrel IUD and the copper T380A. Both are considered appropriate for use in adolescents and nulliparous patients [37]. Neither has been shown to increase the rate of PID or tubal infertility. Both are acceptable for women with a history of ectopic pregnancy or PID [37]. Although the risk of a pregnancy occurring through IUD failure being ectopic is high, the absolute risk of pregnancy is so low that the absolute risk of ectopics is not increased statistically [37]. Expulsion, uterine perforation, and intrauterine pregnancy are also risks, though relatively low. Expulsion may be more common in adolescents and parous women [37].

Testing for STIs is not required before IUD insertion, although testing on the day of insertion is recommended in women who have not been screened for STIs, those at increased risk for STIs, and those with a personal history of STI [37]. A positive test may be treated without removing the IUD [37]. If there is a known STI or mucopurulent discharge at the time of insertion, the infection should be treated before inserting the IUD [37]. PID rates after insertion are the same as for the general population. The increased risk of PID attributed to IUDs appears to be associated with insertion; the risk is only elevated for the first 20 days after insertion. There is no relationship between IUD use and tubal infertility [12]. Routine prophylactic antibiotics at the time of insertion are not recommended [37]. If *Actinomyces* bacteria is noted on a Pap test for a woman with an IUD in place, treatment is not indicated unless the patient is symptomatic, in which case the IUD would be removed and antibiotics given [12]. All IUDs are contraindicated in women with congenital or acquired (e.g., due to fibroids) uterine cavity distortion [18].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Congress/College of Obstetricians and Gynecologists, routine antibiotic prophylaxis to prevent pelvic infection is not recommended before intrauterine device insertion.

(https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2017/11/long-acting-reversible-contraception-implants-and-intrauterine-devices. Last accessed June 15, 2024.)

Level of Evidence: A (Based on good and consistent scientific evidence)

HORMONAL

The levonorgestrel IUD (marketed under the brand names Mirena, Skyla, Liletta, and Kyleena in the United States) is a T-shaped plastic device embedded with levonorgestrel on the long axis. Initially, 14–20 mcg of progesterone are released daily, but this rate slowly decreases to deliver a mean 6–14 mcg/day of progesterone, depending on the brand [18; 37]. The progesterone in the device suppresses the endometrium, induces a weak foreign body reaction, and thickens cervical mucus, which inhibits sperm motility and function [44]. It inhibits ovulation in some, but not all, women [19; 44]. All contraceptive effects of this device occur before implantation of the ovum [37]. The Liletta levonorgestrel IUD is approved in the United States for six years of continuous use; Mirena is used for up to seven years; Kyleena may be used for up to five continuous years; and Skyla is approved for three years of continuous use [18]. The levonorgestrel IUD is very effective contraception, with a one-year failure rate of 0.1 to 0.2 per 100 women [4; 8; 37].

The levonorgestrel IUD can be inserted at any time in the menstrual cycle after confirming that the patient is not pregnant, except in cases of postpartum or postabortion sepsis [23]. A backup method of contraception should be used for seven days, unless the device is inserted within five days of the first day of menses. A backup method is not needed if the device is inserted immediately after childbirth or abortion or if there has been no gap between this method and another hormonal method of contraception [37]. Expulsion rates are higher if the IUD is inserted immediately postpartum (10% to 27%); however, this timing may be considered if there is a high likelihood that the patient will not return for postpartum care or that they may not be able to obtain an IUD in the future. There is no known effect of the levonorgestrel IUD on breastfeeding [37]. IUDs inserted immediately after elective first-trimester abortion have an increased rate of expulsion compared with interval insertions, but if there is doubt as to the patient's returning for follow-up, it is preferable to provide the long-term contraceptive [37]. The insertion of an IUD should be delayed in the case of any known uterine infection, but if an STI is diagnosed after insertion, the IUD does not need to be removed.

The levonorgestrel IUD will decrease menorrhagia resulting from anticoagulation but often will not prevent ovulation. If this is a concern, other methods, such as DMPA, should be considered. Although the levonorgestrel IUD reduces menorrhagia, it is generally not used for bleeding that results from leiomyomata, as these patients tend to have distortion of the uterine cavity. The efficacy does not seem to be affected by antiepileptic or other liver enzyme-inducing medications [19; 23].

This IUD may be a particularly good choice in overweight and obese women, who are at risk for abnormal uterine bleeding and endometrial neoplasia, as the local progesterone effect produced by the IUD can counter both of these risks [19]. It can also be used for endometrial protection for women on estrogen replacement [9]. Weight gain is listed as a potential side effect of the levonorgestrel IUD, although studies have shown weight gain is not clinically significant and occurs in a low percentage of individuals [9; 44].

As the hormone dose is quite low, side effects with the levonorgestrel IUD are minimal. Irregular bleeding is common following insertion, particularly in the first four months, and oligomenorrhea or amenorrhea frequently follow due to the local effect of the progesterone on the endometrium [18]. About 20% of women are amenorrheic by one year of

use, and up to 35% may be oligomenorrheic or amenorrheic immediately after insertion [37]. By 12 months of use, women with menorrhagia experience a 90% reduction in blood loss, although menses return rapidly after removal of the IUD [9; 10]. Side effects such as headaches, depression, nausea, breast tenderness, acne, and ovarian cyst formation can occur [9; 37]. Pregnancy and malignancy must always be included in the differential of any abnormal uterine bleeding [37]. The relative risk for VTE in women using this contraceptive compared with women not on any hormonal medication has been reported to be 0.6 [34].

Any IUD can lead to complications such as expulsion, uterine perforation, and contraceptive failure. If the device fails and pregnancy occurs, it is important to rule out ectopic pregnancy as soon as possible, as ectopic pregnancies occur in 20% of IUD failures [9; 45]. If intrauterine pregnancy occurs with an IUD, the risk for first-trimester spontaneous abortion is increased by a factor of 3, and there are also increases in the risk of septic abortion in the second trimester and preterm birth in the third trimester [45]. The risk for fetal anomalies is not increased [12]. If the strings are visible, the IUD should be removed as early as possible in pregnancy [12]. If perforation into the peritoneal cavity occurs, the device must be removed by laparoscopy or laparotomy [37].

NON-HORMONAL

The copper T380A is marketed under the brand name ParaGard in the United States. It is a T-shaped plastic device wrapped in copper wire along both arms and the long axis [37]. It is approved for 10 years of continuous use in the United States [18].

The device has several proposed mechanisms of action, including inhibition of ovum transportation speed, damage to the ovum itself, and impairment of sperm motility and viability [9; 18; 37]. It is also possible that the fertilized ovum can be damaged before implantation, although pre-fertilization effects are thought to be the primary mechanisms of action. The copper IUD can be used as effective emergency contraception before implantation occurs up to five days after unprotected intercourse [22]. As noted, the IUD can be used for 10 years and has a 1-year failure rate of 0.6 to 1.0 per 100 women and a 10-year failure rate of 1.9 per 100 women [4; 8; 37]. The failure rate of the copper IUD may be higher in younger women than older women [45].

The copper IUD can be inserted at any time in the menstrual cycle after confirming that the patient is not pregnant, except in cases of postpartum or postabortion sepsis [23]. A backup method of contraception is not needed. Expulsion rates are higher in adolescents and parous women and if the IUD is inserted immediately postpartum or after first-trimester abortions, but it may be considered based on patient-related factors [37]. There is no known effect of the copper IUD on breastfeeding. The insertion of an IUD should be delayed if a patient has a current uterine infection, but it does not need to be removed if an STI is diagnosed after insertion [9].

Irregular bleeding, cramping, heavier menses, and dysmenorrhea, along with pain on insertion, are the most common side effects [4; 9]. Heavy menses and dysmenorrhea do decrease over time, although intermenstrual spotting and pain do not decrease. Pregnancy and malignancy should always be included in the differential of any abnormal uterine bleeding [37].

As discussed, IUD use can lead to complications such as expulsion, uterine perforation, contraceptive failure, and ectopic pregnancy [9; 45]. The copper IUD should not be used in women with copper allergies or Wilson disease. It should be employed with caution in women with already heavy menses [9; 23].

STERILIZATION

Sterilization is the most common form of contraception in the United States, with female sterilization more common than male, ranking only slightly below the use of the oral contraceptive pill in terms of overall usage [8; 12; 45]. Sterilization is the most common method in black and Hispanic women, women older than 35 years of age, ever-married women, women with two or more children, women living below 150% of the federal poverty level, women with less than a college education, women living outside of a metropolitan area, and those with public or no health insurance [8]. In contrast, oral contraceptives are the most common method in white women, women in their teens and 20s, never-married and cohabiting women, childless women, and college graduates [8]. There are new, minimally invasive methods of achieving female sterilization. However, these methods are not without drawbacks, including delayed time for full effectiveness.

Tubal sterilization can be performed postpartum or following a spontaneous or induced abortion. About half of the time, it is performed as an interval procedure, unrelated in its timing to pregnancy [45]. Before any sterilization procedure takes place, the patient must be counseled that there remains a failure rate and that menses will continue, as will the need for pelvic exams and Pap tests [12].

As tubal sterilization is a permanent form of contraception, a thorough discussion of all the risks and benefits, stressing the permanent nature of the procedure, must be conducted with the patient before coming to the decision to perform sterilization. Studies have shown that the chance of future regret is higher in women who are younger at the time of their sterilization, with the age of decreasing regret occurring at 30 years of age [12; 45].

If a pregnancy occurs after any method of tubal sterilization, the patient must be evaluated for ectopic pregnancy. An intrauterine pregnancy can also occur after tubal sterilization.

Many women report menstrual changes after sterilization, but these are thought to be the result of discontinuing previous forms of contraception. There have been no study results supporting this claim [12; 45].

There appears to be a beneficial effect of tubal sterilization on the development of ovarian cancer (except in women with *BRCA* mutations). For many speculative reasons, hysterectomy rates are four to five times higher in women who have had tubal ligation; however, this seems to be associated with a preprocedure history of menstrual disorders and other benign gynecologic disorders (e.g., endometriosis, uterine fibroids). [12; 45]. Tubal sterilization is protective against PID, but it has no effect on breast or endometrial cancer or bone density [12].

SURGICAL

Surgical sterilization is often performed postpartum, either at the time of cesarean delivery, when it is easily added to the procedure, or following vaginal delivery by minilaparotomy. The procedure is often conducted under regional anesthetic, although it can be performed under general or local anesthetic with sedation [45]. Any surgical sterilization method carries the risks of anesthesia, as well as bleeding, organ or blood vessel injury, and death [12].

There are many different techniques for ligating the fallopian tube at minilaparotomy, largely coming down to physician training and preference. Fimbriectomy can also be performed. Regardless of which method is chosen, care must be taken to ligate the entire tubal lumen and to visualize fimbriae in order to ensure it is the tube, and not the round ligament, that is being manipulated [4; 45]. If a segment of tube is removed, as it is with most laparotomy methods, it must be sent to pathology for evaluation of complete transaction [4; 45].

Laparoscopy is usually used for post-abortion or interval tubal sterilization. It results in a smaller surgical scar than minilaparotomy, although there are at least two incisions, with the attendant risk for organ or vessel injury with each trochar insertion [45]. There are also the risks of general anesthesia, necessary for laparoscopy, to consider with this method. There is also no pathologic specimen to send for confirmation of complete transaction. Methods of tubal occlusion with laparoscopy include coagulation with bipolar cautery, which is probably the most common method. At least 3 cm of the isthmic tube must be thoroughly cauterized [12; 45]. Mechanical devices can also be applied to the tube during laparoscopy; these include silicone rubber bands and metal clips. There is a small risk of clip or band migration or expulsion with the mechanical methods, but these methods cause less destruction to the tube, making surgical reversal an easier option should the patient express regret at a later time [12; 45]. Patients wishing for surgical tubal ligation reversal should have a detailed conversation with a reproductive specialist about the pros and cons of the surgery versus in vitro fertilization.

Failure rates are low with surgical sterilization methods, but pregnancies can occur. If a pregnancy occurs after tubal sterilization, the patient must be evaluated for ectopic pregnancy. One-third of sterilization failures are ectopic pregnancies [12; 45]. An intrauterine pregnancy can also occur after tubal sterilization, but unlike with IUDs, there is no known risk to the mother or fetus. Taken together, surgical sterilization failure rates range from 7.5 to 36 per 1,000 procedures. Postpartum partial salpingectomy has the lowest failure rate [45].

HYSTEROSCOPIC (DISCONTINUED)

No hysteroscopic sterilization devices are available as of 2021 [45]. In 2002, the Essure device was approved in the United States for hysteroscopic sterilization [45]. However, based on reports of adverse events from patients and clinicians, the FDA held a postmarket panel meeting in 2015 to re-evaluate the benefits and risks [46; 47]. Reported adverse events included implant perforation and migration, chronic pain, allergic reactions, irregular bleeding, and unintended pregnancy. Essure was removed from the market in 2018 [57].

Another transcervical hysteroscopic device, Adiana, was approved in 2009 [12]. Rather than a metal coil, this method used a soft polymer insert and delivered bipolar radiofrequency energy to damage a small portion of the fallopian tube at the insert site. Tissue then grew into the matrix of the insert. With a high failure and complication rate, the manufacturer of Adiana discontinued its production in 2012 [48].

Patients who received these devices who never had a follow-up to check for proper placement should be advised to undergo hysterosalpingography or transvaginal ultrasonography to confirm bilateral tubal sterilization, as the failure rate is higher in this group [45]. Persons who are experiencing complications suspected of being related to one of these devices and for whom conservative treatment options have failed should be counseled about the risks and benefits of surgical device removal. Cornuectomy, hysteroscopic removal, and laparoscopic salpingectomy have been successful; hysterectomy is not typically necessary or recommended unless otherwise indicated [45].

MALE STERILIZATION

Vasectomy is a commonly performed surgical procedure, and it is safely done in the office under local anesthesia. It is safer and less expensive than female surgical sterilization, although less commonly performed (17% of sterilizations) [12; 45]. Failure rates are less than 2% [4; 45].

Complications such as bleeding, hematoma, and epididymitis can occur. No-scalpel techniques, wherein the scrotum is punctured but no scalpel incision is made, carry lower risks of bleeding and infection [4; 12; 45]. Men are not immediately infertile after vasectomy. Infertility must be confirmed by semen analysis and can take around three months to be complete [12; 45].

POSTPARTUM CONTRACEPTION

Women who are exclusively breastfeeding will usually not ovulate for at least three months postpartum, although non- or partially breastfeeding women may ovulate as early as three weeks postpartum [12]. Women can have a false sense of security after giving birth and may not realize they can become pregnant.

This can be a problem, as short inter-pregnancy intervals can lead to low birth weight and preterm deliveries [23].

Progesterone-only contraceptive methods, such as DMPA and progestin-only pills, may be used immediately postpartum as they do not increase coagulability or have effects on breast milk [12; 19]. It is advised to wait four to six weeks before beginning COCs or other estrogen-containing methods due to the risk of clot from estrogen products and from the pregnancy/puerperium itself [19]. Some sources advise waiting six months if the woman is breastfeeding [12]. COCs have not been shown to impact infant development in well-nourished lactating women, although they may have effects on milk production and content [12; 19].

It is advisable to wait four to six weeks for IUD insertion to avoid expulsion, although IUDs may be inserted sooner, even immediately after delivery, if the contraceptive benefits outweigh the risks [9; 37]. Delayed postpartum insertion (i.e., at the postpartum visit) is commonplace. If there has been a uterine infection with delivery or in the puerperium, it is advisable to wait three months before inserting an IUD [19; 23]. Condoms may be used postpartum without a waiting period; other barrier methods should be delayed for six weeks [23].

EMERGENCY CONTRACEPTION

Emergency contraception, as an FDA-approved entity, is a relatively new phenomenon, approved in 1998. Research on it began, however, in the 1960s, when it was first used as a treatment for rape victims, and the first published article on a combination oral regimen (now known as the Yuzpe method) was seen in 1974 [4; 22]. When emergency contraception was first available, both patient and clinician knowledge was severely lacking; however, since the late 1990s, information has become more readily available, and several states have enacted legislation to provide easier access to and information about emergency contraception. Healthcare providers have historically been poorly informed or reluctant to give information on emergency contraception to their patients. As a result of these and a variety of other factors, approximately 40% of patients are unaware that emergency contraception exists; the rate is even higher among those born outside the United States, in lower socioeconomic statuses, and those who never completed high school [22].

The CDC's National Survey of Family Growth, conducted between 2006 and 2010, reported that in 1995, 1% of sexually experienced women between 15 to 44 years of age had ever used emergency contraception. That number grew to 4.2% in 2002 and to 11% (5.8 million women) between 2006 and 2010. Of the 11%, 59% had used some form of emergency contraception once, 24% had used it twice, and 17% had used it three or more times [64]. When broken down by age, adults 20 to 24 years of age were most likely to use emergency contraception (23%), followed by women 25 to 29 years of age (16%), adolescents 15 to 19 years of age (14%), and finally women 30 to 44 years of age (5%). In addition, more users of emergency contraception have never been married (19%) or are currently cohabiting (14%), compared with women who are currently or formerly married (6%) [64].

Postcoital contraception is synonymous with emergency contraception. Most methods are effective up to five days after unprotected intercourse [12; 22; 50; 52]. They may be used when intercourse has not been protected by any contraceptive, when contraception was not properly used (e.g., missed oral contraceptive pills, nonconsensual condom removal or "stealthing"), or when contraceptive methods failed (e.g., broken or slipped condoms) [50]. Progestin-only emergency contraceptives are available over the counter without a prescription. Although they are recommended for people 17 years of age and older, no proof of age is necessary for purchase and they are available for people of any age [50]. Despite being theoretically available in pharmacies without a prescription, the products are relatively expensive ($40 to $50 on average) and are typically kept behind the counter, require a pharmacist consultation, or are in locked cases, which deters use, particularly for younger persons [22; 52]. A 2015 survey found emergency contraception was stocked in only 64% of pharmacies, and a 2019 "secret-shopper" review found emergency contraception in only 69% of pharmacies visited, although the authors noted increasing availability [43; 52].

Many of the contraceptive methods described in this educational activity can be used off-label as emergency contraception, including COCs, progesterone-only pills, and the copper IUD. More rarely, estrogen-only or antiprogestin methods (such as mifepristone) can be used [4; 22; 51; 52]. The most common methods used in the United States have been progestin-only and COC methods; however, ulipristal acetate (UPA), a single-dose (30 mg) progesterone-receptor modulator, is a newer option and also the most effective oral emergency contraceptive [22; 51; 52]. UPA was approved for emergency contraception in 2010 and is only available by prescription.

The combined method of emergency contraception is no longer sold as a dedicated product, and it is no longer recommended due to the availability of more effective options with fewer adverse effects [22]. However, it can be prescribed if necessary. This option comprises two doses taken 12 hours apart, each with 100 mcg of ethinyl estradiol and 0.5 mg of levonorgestrel. The progestin-only method can be taken as one dose of 1.5 mg levonorgestrel (preferred) or two doses of 0.75 mg levonorgestrel taken 12 hours apart (although the second dose can be taken up to 24 hours after the first dose) [18; 22]. The first dose should be taken as soon as possible after unprotected intercourse, up to five days later [51; 52]. Although the package inserts advise use by 72 hours, studies have shown effectiveness with the first dose taken by 120 hours [22; 52]. Emergency contraception is more effective the sooner it is taken after intercourse [18].

Again, UPA is the most effective pill form of emergency contraception (1.4% pregnancy rate) [22]. The progestin-only regimens (2.2% pregnancy rate) are more effective than combined regimen. All methods have greatest efficacy when taken as soon after unprotected intercourse as possible [22]. If a patient does not have access to UPA or the progestin-only method, they can use an existing oral contraceptive to make up the appropriate dosage for emergency contraception. The copper IUD may also be used as emergency contraception; it is inserted as soon as possible up to five days after unprotected intercourse [22; 50; 66]. The pregnancy rate with this approach is approximately 0.1%. The copper IUD acts by impairing fertilization, altering sperm motility, and impairing implantation [50; 66].

As the UPA and progestin-only pills have fewer side effects (mainly less nausea and vomiting) and are more effective, they are recommended by ACOG [22]. All hormonal methods are capable of inhibiting ovulation or delaying ovulation, depending on the timing of the dose in relation to the menstrual cycle. It is also theorized that these medications can alter the endometrial lining, inhibit sperm transport, or interfere with the functioning of the corpus luteum. However, the data have not consistently supported these theories. Emergency contraception is ineffective after pregnancy is established; it is not an abortifacient, and it is not teratogenic [12; 22].

The most common side effect is nausea and vomiting, particularly with combination methods [18; 50]. An antiemetic given one hour before taking the combination dose can help to alleviate this side effect [50]. If vomiting occurs within two to three hours of emergency contraception ingestion, the dose should be repeated. Severe or persistent vomiting can be addressed with vaginal administration of the emergency contraception tablets, which does not impair their absorption. Irregular bleeding is also common, lasting from one day to one month after emergency contraception [18]. The next menstrual period is commonly either hastened or delayed by one week from the expected time. Less frequent side effects can include breast tenderness, abdominal pain, fatigue, headache, and dizziness [18]. There have never been any reports of deaths or severe complications from emergency contraception [22].

Emergency contraception has no effect on the risk of subsequent ectopic pregnancy [12; 22]. It may also be used in any woman who has had a previous ectopic pregnancy and in women with other contraindications to combined oral contraceptives, such as migraines, cardiovascular disease, and liver disease. Emergency contraception may be used while breastfeeding [22].

A physical exam or pregnancy test is not required before dispensing emergency contraception [52]. A follow-up exam is also not required [22]. However, if menses have not occurred by one week after the expected time or within 21 days of emergency contraception use or if abdominal pain or bleeding are persistent, the patient should be evaluated [12; 22].

When a woman presents to her healthcare provider for emergency contraception, it can be a good opportunity to discuss more reliable, long-term forms of contraception. It is also an opportunity to offer testing for STIs. It is important that any victim of sexual assault be offered emergency contraception; as noted, in some states this is required by law [12; 63; 65]. Long-term contraception should be initiated immediately after emergency contraception (in cases where a copper IUD was not used), as a woman can become pregnant later in the same cycle. Emergency contraception may be repeated more than once in the same cycle. Any non-barrier method of birth control may be initiated either immediately (with a barrier back-up method) or at the next menstrual period. Long-term methods, such as the progesterone injection, implant, or hormonal IUD, should be delayed until the next menstrual period confirms that the patient is not pregnant [22].

The Faculty of Sexual and Reproductive Healthcare asserts that patients should be advised that oral emergency contraceptive methods do not provide contraceptive cover for subsequent unprotected sexual intercourse and that they will need to use contraception or refrain from sex to avoid further risk of pregnancy.

(https://www.fsrh.org/documents/ceu-clinical-guidance-emergency-contraception-march-2017. Last accessed June 15, 2024.)

Level of Evidence: B (Robust experimental or observational studies)

An analysis published in 2015 found that only 21% to 50% of sexual assault victims were given or offered emergency contraception in the emergency department [22]. Since then, nearly one-half of all states have enacted legislation requiring hospital emergency departments to provide emergency contraception-related information to sexual assault victims, and nearly one-third of states and the District of Columbia require healthcare providers to dispense the drug on request to victims [65]. In addition, some states allow pharmacists to initiate emergency contraception if working in collaboration with a physician or without a prescription after completing a training program [63]. Another study found that 0% to 65% of adolescent sexual assault patients are being provided with emergency contraception in American emergency departments, despite the majority visiting the hospital within 72 hours of the assault [49].

Studies have shown that people are more likely to use emergency contraception if they have a prescription or the pills at the time of unprotected intercourse [12; 22; 52]. It has also been shown that retaining emergency contraception does not lead to increased/risky sexual activity or more frequent unintended pregnancy. The American Academy of Pediatrics

recommends that pediatricians provide adolescent patients with an advanced provision of emergency contraceptive (i.e., a supply of progesterone-only or UPA pills or a prescription, with refills, of the same) in addition to condoms [52]. This same recommendation applies to any physician providing care for patients who may become pregnant. All patients should receive education regarding the availability of emergency contraception, and a prescription for emergency contraception should be offered as part of routine gynecological visits [22]. In its guideline, the American Academy of Pediatrics also notes that pharmacists and prescribers have a duty to provide access to relevant and legally available treatments, even if they have personal objections or to offer a referral to another provider who will provide those services [52].

MALE CONTRACEPTIVE PILL

There are newer contraceptive methods in the pipeline, such as the much-publicized but not-yet-seen male contraceptive pill. Systemic male contraceptives have proven tricky. As men are continuously producing sperm, the physiology of contraception is not as straightforward as it is in women. Possible approaches include blocking hormonal control over testicular cell function, stopping sperm production by altering seminiferous tubule function, and blocking maturation, functioning, or transport of sperm [4]. Side effects and acceptability must also be taken into account.

There have been reported studies on a new transdermal gel for men, containing testosterone and progestin. Preliminary research showed that it reduced sperm concentration to ≤1 million/mL [53].

Another novel oral contraceptive option for men is dimethandrolone undecanoate (DMAU), which is converted to dimethandrolone (DMA), an ester and prodrug that binds to androgen and progesterone receptors, suppresses gonadotropins, maintains androgenic effects, and inhibits spermatogenesis in pre-clinical studies [67]. Research results have been encouraging, showing a reduction of serum testosterone to near castrate levels, without significant side effects. Continued research is necessary to determine the safety and efficacy of this drug as a successful male contraceptive [67].

Attitudes toward the male contraceptive pill have been less favorable than those toward female contraceptive pills, with women more positive than men [54]. However, this appears to be changing. A study conducted by the Kaiser Foundation found that 66% of men were willing to take a birth control pill, 44% were willing to take a birth control shot, and 36% were interested in the idea of an implant [55; 56]. Women have expressed concern regarding male adherence to regimens and less perceived engagement in the consequences of unintended pregnancies.

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

Because selecting the appropriate contraception is linked so closely to patient-related factors and wishes, communication is a vital aspect of the process. The patient population in the United States is diverse and becoming more so. Therefore, consideration should be given to those patients who are not proficient in spoken and/or written English. When there is an obvious disconnect in the communication process between the practitioner and patient, an interpreter is required.

In this multicultural landscape, interpreters are 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, interpreters serve as cultural brokers who ultimately enhance the clinical encounter. When providing care for patients for whom English is a second language, consideration of the use of an interpreter and/or patient education materials in their native language may improve patient understanding and outcomes.

CONCLUSION

Different contraceptive methods abound—from natural family planning techniques to hormonal contraception to sterilization. The range of hormonal methods is vast and growing rapidly. COCs remain extremely popular among patients, but new doses, delivery vehicles, and formulations make staying current on these methods a challenge. The wide selection of progesterones in oral contraceptive pills complicates selecting a pill based on the desired side-effect profile. The wide range of contraceptive options, as well as newer contraceptive methods on the market, can pose a challenge when attempting to advise patients and address their concerns. All healthcare professionals should have a clear understanding of the contraceptive options available and how they may impact patient health and quality of life.

COURSE TEST - #93113 CONTRACEPTION

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 December 31, 2025.

1. Of the following natural family planning methods, which has the lowest first-year failure rate?
- A) *Ovulation method*
- B) *Symptothermal method*
- C) *Calendar rhythm method*
- D) *Both B and C*

2. According to Table 1, which of the following shows a different efficacy in parous versus nulliparous women?
- A) *Withdrawal*
- B) *Copper IUD*
- C) *Tubal sterilization*
- D) *Contraceptive sponge*

3. Which of the following methods of hormonal contraception has the lowest failure rate with typical use?
- A) *Female condom*
- B) *Levonorgestrel IUD*
- C) *Progestin-only pills*
- D) *Combined oral contraceptive pills*

4. Which of the following is TRUE regarding use of the diaphragm?
- A) *It should not be used with spermicide.*
- B) *It must be fitted by a healthcare provider.*
- C) *The device must be left in place for 24 hours after intercourse.*
- D) *All of the above*

5. After intercourse, the contraceptive sponge must be left in place for
- A) *1 hour.*
- B) *6 hours.*
- C) *12 hours.*
- D) *24 hours.*

6. The estrogen component of combined oral contraceptives
- A) *thickens cervical mucus.*
- B) *inhibits FSH production.*
- C) *provides the main contraceptive effect.*
- D) *potentiates the luteinizing hormone surge.*

7. Androgenic progestins may have which of the following side effects?
- A) *Acne*
- B) *Nausea*
- C) *Breast tenderness*
- D) *Beneficial lipid profile effects*

8. Oral contraceptives differ in their progestin components. Which progestin has been associated with a possibly higher risk of venous thromboembolism?
- A) *Desogestrel*
- B) *Norgestimate*
- C) *Levonorgestrel*
- D) *Norethindrone*

9. According to the American Congress/College of Obstetricians and Gynecologists, progestin-only or nonhormonal contraceptive methods may be safer for women with
- A) *hypotension.*
- B) *coronary artery disease.*
- C) *lupus without vascular disease.*
- D) *a history of smoking before age 20 years.*

10. Combined oral contraceptives should NOT be used in women with
- A) *severe liver disease.*
- B) *symptomatic gallbladder disease.*
- C) *undiagnosed genital tract bleeding.*
- D) *All of the above*

Test questions continue on next page ➞

11. The progesterone depot injection may cause
- A) *anemia.*
- B) *dysmenorrhea.*
- C) *improvement in endometriosis symptoms.*
- D) *an increase in seizures in patients with seizure disorders.*

12. All of the following are possible side effects of the progesterone injection, EXCEPT:
- A) *Amenorrhea*
- B) *Ovarian cysts*
- C) *Bone density loss*
- D) *Increased low-density lipoprotein cholesterol*

13. IUDs carry all of the following risks, EXCEPT:
- A) *Ectopic pregnancy*
- B) *Uterine perforation*
- C) *Intrauterine pregnancy*
- D) *Tubal infertility through pelvic inflammatory disease*

14. Which of the following is NOT recommended at the time of IUD insertion?
- A) *Prophylactic antibiotic administration*
- B) *Backup contraceptive provision/discussion*
- C) *Discussion of side effects regarding bleeding patterns*
- D) *Screening for sexually transmitted infections in women with risk factors*

15. The copper IUD
- A) *has no known effect on breastfeeding.*
- B) *must be inserted within five days of the last menses.*
- C) *is approved for a maximum of three years of continuous use.*
- D) *should be removed if a sexually transmitted infection is diagnosed.*

16. Hysteroscopic sterilization
- A) *is the safest form of permanent contraception.*
- B) *has no known adverse effects.*
- C) *is easily reversed.*
- D) *is no longer performed due to removal from the market.*

17. Which of the following methods of contraception should NOT be initiated immediately postpartum?
- A) *Condoms*
- B) *Diaphragm or cervical cap*
- C) *Progesterone-only methods*
- D) *None of the above*

18. Estrogen-containing contraceptives are not advised within six weeks of delivery because they
- A) *may increase milk supply.*
- B) *raise the risk for blood clot.*
- C) *increase the risk of uterine infection.*
- D) *negatively impact infant development.*

19. Which of the following options may be used for emergency contraception?
- A) *Copper IUD*
- B) *Progesterone-only pills*
- C) *UPA*
- D) *All of the above*

20. Which of the following statements regarding restrictions in the use of emergency contraception is TRUE?
- A) *It may not be repeated in the same menstrual cycle.*
- B) *The oral methods will not disrupt an established pregnancy.*
- C) *It is contraindicated in women who have had an ectopic pregnancy.*
- D) *A physical exam should be performed before prescribing emergency contraception.*

Child, Adolescent, and Adult Immunization Schedules

This course meets the California requirement for immunizations and vaccines education.

Audience

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

Course Objective

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

Learning Objectives

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

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

Faculty

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

Faculty Disclosure

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

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Division Planner/Director Disclosure

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

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INTRODUCTION

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

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

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

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

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

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

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

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

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

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

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

AN OVERVIEW OF IMMUNIZATION SCHEDULES

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

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

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

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

THE CHILD AND ADOLESCENT IMMUNIZATION SCHEDULE

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

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

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

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

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

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

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

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

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

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

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

Source: [12] *Table 2*

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

Table 3 continues on next page

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

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

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

Source: [12] *Table 3*

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

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

Source: [19] *Table 4*

THE ADULT IMMUNIZATION SCHEDULE

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

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

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

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

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

VACCINES AND RECOMMENDATIONS

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

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

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

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

Source: [19] *Table 5*

SEASONAL INFLUENZA

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

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

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

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

Level of Evidence: Expert Opinion/Consensus Statement

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

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

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

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

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

TETANUS/DIPHTHERIA/PERTUSSIS

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

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

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

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

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

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

HUMAN PAPILLOMAVIRUS

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

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

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

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

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

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

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

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

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

ROTAVIRUS

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

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

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

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

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

MENINGOCOCCAL DISEASE

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

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

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

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

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

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

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

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

HEPATITIS A

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

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

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

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

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

HERPES ZOSTER

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

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

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

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

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

PNEUMOCOCCAL VACCINES

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

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

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

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

Level of Evidence: Expert Opinion/Consensus Statement

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

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

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

RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINATION

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

Recommendation for Adults: One dose RSV vaccine is recommended for all pregnant patients at 32 to 36 weeks' gestation from September through January in most of the continental United States, regardless of previous RSV infection. Based on shared clinical decision-making, one dose RSV vaccine may be administered to patients 60 to 74 years of age. One dose RSV vaccine is recommended for all patients 75 years of age and older with no evidence of immunity.

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

Vaccination with a single RSV vaccine dose has demonstrated moderate-to-high efficacy in preventing symptomatic RSV-associated lower respiratory tract disease among adults 60 years of age or older. In 2024, the ACIP added a recommendation for RSV vaccination for older adults based on shared clinical decision-making and generally for all patients 75 years of age and older [123]. Persons 60 years of age and older who are most likely to benefit from vaccination include those with chronic medical conditions (e.g., lung diseases, cardiovascular diseases, neurologic or neuromuscular conditions, kidney disorders, liver disorders, hematologic disorders, diabetes, and moderate or severe immune compromise); those who are considered to be frail; those of advanced age; those who reside in nursing homes or other long-term care facilities; and those with other underlying medical conditions or factors that a healthcare provider determines might increase the risk of severe respiratory disease [122].

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

In general, the timing of RSV vaccination is based on the seasonal patterns of RSV disease transmission. Providers in jurisdictions with RSV seasonality that differs from most of the continental United States (e.g., Alaska, tropical climates) should follow guidance from public health authorities or regional medical centers on timing of administration based on local RSV seasonality [12; 19].

VACCINE CONTRAINDICATIONS

GENERAL INFORMATION

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

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

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

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

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

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

ALLERGY/HYPERSENSITIVITY

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

IMMUNODEFICIENCY

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

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

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

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

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

PREGNANCY

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

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

TUBERCULOSIS

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

HISTORY OF GUILLAIN-BARRÉ SYNDROME

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

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

OTHER ISSUES

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

Rotavirus Vaccine and Gastrointestinal Disease

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

DTaP, Tdap, and Neurologic Events

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

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

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

DTaP, Tdap, Td, and Arthus Reactions

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

Vaccines Containing Diphtheria or Tetanus Components

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

Influenza (LAIV) and Acute or Chronic Illness

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

PPSV Considerations

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

VACCINE SAFETY

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

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

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

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

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

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

MMR AND AUTISM

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

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

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

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

THIMEROSAL AND AUTISM

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

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

MULTIPLE VACCINES AND THE IMMUNE SYSTEM

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

ROTAVIRUS VACCINES AND INTUSSUSCEPTION

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

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

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

INFLUENZA VACCINE AND GUILLAIN-BARRÉ SYNDROME

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

MCV AND GUILLAIN-BARRÉ SYNDROME

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

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

HPV VACCINE AND ADVERSE EVENTS

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

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

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

OVERCOMING BARRIERS FOR CHILDREN AND ADOLESCENTS

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

EDUCATING PARENTS ABOUT VACCINES AND VACCINE SAFETY

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

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

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

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

Because patient education is such a vital aspect of vaccine promotion, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter.

REDUCING THE NUMBER OF INJECTIONS

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

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

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

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

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

ADDRESSING CONCERNS ABOUT VACCINE COSTS

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

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

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

INSTITUTING REMINDER SYSTEMS

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

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

OVERCOMING BARRIERS FOR ADULTS

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

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

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

REDUCING "MISSED OPPORTUNITIES" FOR ADULTS

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

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

REMINDER SYSTEMS FOR ADULT PATIENTS

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

CONCLUSION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Test questions continue on next page ➞

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

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

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

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

17. Research regarding parents' concerns about vaccination suggests that

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

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

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

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

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

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

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

Opioid Safety: Balancing Benefits and Risks

This course meets the California requirement for education on the risks of addiction associated with Schedule II drugs as well as the use of nalaxone hydrochloride for those who prescribe these medications.

Audience

This course is designed for all pharmacy professionals, physicians, osteopaths, physician assistants, and nurses who may alter prescribing and/or dispensing practices to ensure safe opioid use.

Course Objective

The purpose of this course is to provide clinicians who prescribe or distribute opioids with an appreciation for the complexities of opioid prescribing and the dual risks of litigation due to inadequate pain control and drug diversion or misuse in order to provide the best possible patient care and to prevent a growing social problem.

Learning Objectives

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

1. Outline the types of pain and effective approaches to managing different pain types.
2. Describe the Centers for Disease Control and Prevention's most recent guidelines for prescribing opioids.
3. Identify behaviors that are indicative of opioid seeking, diversion, addiction, and/or misuse.
4. Discuss federal and state laws pertaining to the prescription of controlled substances.
5. Create a plan to properly educate patients and families regarding safe opioid use.
6. Describe effects of, potential causes of, and approaches to minimize disparities in pain management.

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. (A complete biography can be found at NetCE.com.)

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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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

Healthcare professionals should know the best clinical practices in opioid prescribing, including the associated risks of opioids, approaches to the assessment of pain and function, and pain management modalities. Pharmacologic and nonpharmacologic approaches should be used on the basis of current knowledge in the evidence base or best clinical practices. Patients with moderate-to-severe chronic pain who have been assessed and treated, over a period of time, with nonopioid therapy or nonpharmacologic pain therapy without adequate pain relief, are considered to be candidates for a trial of opioid therapy [1; 2]. Initial treatment should always be considered individually determined and as a trial of therapy, not a definitive course of treatment [3].

TYPES OF PAIN AND THE ROLE OF OPIOIDS

ACUTE AND SUBACUTE PAIN

Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute (less than one month) or subacute (one to three months) pain, clinicians should prescribe the lowest effective dose of immediate-release opioids in a quantity no greater than that needed for the expected duration of severe pain [2; 4].

With postoperative, acute, or intermittent pain, analgesia often requires frequent titration, and the two- to four-hour analgesic duration with short-acting hydrocodone, morphine, and oxycodone is more effective than extended-release formulations. Short-acting opioids are also recommended in patients who are medically unstable or with highly variable pain intensity [5; 6; 7].

CHRONIC PAIN

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

interactive activity

View the CDC's video Prescription Opioids: Back on Track at https://youtu.be/EfojmJtnvFU. This video highlights the risks of opioids and offers some nonopioid options for chronic pain management.

Implantable intrathecal opioid infusion and/or spinal cord stimulation may be options for severe, intractable pain. Both options require that devices or ports be implanted, with associated risks. With intrathecal opioid infusion, the ability to deliver the drug directly into the spine provides pain relief with significantly smaller opioid doses, which can help to minimize side effects (e.g., drowsiness, dizziness, dry mouth, nausea, vomiting, and constipation) that can accompany systemic pain medications that might be delivered orally, transdermally, or through an IV [8]. However, use of opioid infusion has traditionally been limited to cancer pain. With spinal cord stimulation therapy, the most challenging aspect is patient selection. In order for patients to be considered for spinal cord

stimulation, other options should have been ineffective or be contraindicated. Spinal cord stimulation is indicated for severe neuropathic pain persisting at least six months.

If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate. Clinicians should consider opioid therapy only if expected benefits for pain and function are anticipated to outweigh risks to the patient [2; 4].

Opioid therapy for chronic pain should be presented as a trial for a pre-defined period (e.g., ≤30 days). The goals of treatment should be established with all patients prior to the initiation of opioid therapy, including reasonable improvements in pain, function, depression, anxiety, and avoidance of unnecessary or excessive medication use [2; 9]. The treatment plan should describe therapy selection, measures of progress, and other diagnostic evaluations, consultations, referrals, and therapies.

In patients who are opioid-naïve, start at the lowest possible dose and titrate to effect. Dosages for patients who are opioid-tolerant should always be individualized and titrated by efficacy and tolerability [2; 9]. When starting opioid therapy for chronic pain, clinicians should prescribe short-acting instead of extended-release/long-acting (ER/LA) opioid formulations [2; 4].

The need for frequent progress and benefit/risk assessments during the trial should be included in patient education. Patients should also have full knowledge of the warning signs and symptoms of respiratory depression. Prescribers should carefully reassess evidence of benefits and risks when increasing the dosage to ≥50 mg morphine milligram equivalents (MME) per day. In its 2016 guideline, the CDC recommended that decisions to titrate dose to ≥90 mg MME/day should be avoided or carefully justified [2; 10]. This recommendation does not appear in the 2022 revision.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Society of Interventional Pain Physicians, before starting opioid therapy, clinicians must take certain basic steps to prevent opioid abuse: distinguish individual opioid abuse risk factors; screen patients' potential for addiction and abuse during their initial visit; categorize patients in accordance with their level of risk and implement an appropriate level of monitoring; and refrain from judgments before a thorough assessment. Combining the above strategies with point-of-care urine drug testing as a confirmatory tool have been shown to contribute significantly to the identification of inconsistencies.

(https://www.painphysicianjournal.com/current/pdf?article=NDIwNA%3D%3D&journal=103. Last accessed September 21, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

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 [11].

PALLIATIVE CARE AND PAIN AT THE END OF LIFE

Unrelieved pain is the greatest fear among people with a life-limiting disease, and the need for an increased understanding of effective pain management is well-documented [12]. Although experts have noted that 75% to 90% of end-of-life pain can be managed effectively, rates of pain are high, even among people receiving palliative care [12; 13; 14; 15].

The inadequate management of pain is the result of several factors related to both patients and clinicians. In a survey of oncologists, patient reluctance to take opioids or to report pain were two of the most important barriers to effective pain relief [16]. This reluctance is related to a variety of attitudes and beliefs [12; 16]:

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

Education and open communication are the keys to overcoming these barriers. Every member of the healthcare team should reinforce accurate information about pain management with patients and families. The clinician should initiate conversations about pain management, especially regarding the use of opioids, as few patients will raise the issue themselves or even express their concerns unless they are specifically asked [17]. It is important to acknowledge patients' fears individually and provide information to help them differentiate fact from fiction. For example, when discussing opioids with a patient who fears addiction, the clinician should explain that the risk of addiction is low [12]. It is also helpful to note the difference between addiction and physical dependence.

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

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

- Explain that pain and severity of disease are not necessarily related.

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

Clinicians' attitudes, beliefs, and experiences also influence pain management, with addiction, tolerance, side effects, and regulations being the most important concerns [12; 14; 16; 18]. A lack of appropriate education and training in the assessment and management of pain has been noted to be a substantial contributor to ineffective pain management [16; 18]. As a result, many clinicians, especially primary care physicians, do not feel confident about their ability to manage pain in their patients [16; 18].

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

Strong opioids are used for severe pain at the end of life [13; 14]. Morphine, buprenorphine, oxycodone, hydromorphone, fentanyl, and methadone are the most widely used in the United States [19]. Unlike nonopioids, opioids do not have a ceiling effect, and the dose can be titrated until pain is relieved or side effects become unmanageable. Patients who are opioid-naïve or who have been receiving low doses of a weak opioid, the initial dose should be low, and, if pain persists, the dose may be titrated up daily until pain is controlled.

More than one route of opioid administration will be needed by many patients during end-of-life care, but in general, opioids should be given orally, as this route is the most convenient and least expensive. The transdermal route is preferred to the parenteral route, although dosing with a transdermal patch is less flexible and so may not be appropriate for patients with unstable pain [14]. Intramuscular injections should be avoided because injections are painful, drug absorption is unreliable, and the time to peak concentration is long [14].

CENTERS FOR DISEASE CONTROL AND PREVENTION OPIOID PRESCRIBING GUIDELINE

The Centers for Disease Control and Prevention (CDC) originally published *Guideline for Prescribing Opioids for Chronic Pain–United States, 2016* in an effort to address an ongoing crisis of prescription opioid misuse, abuse, and overdose [2]. While these guidelines were based on the best available evidence at the time, there was some criticism that they were too focused on limiting opioid prescriptions—to the point of patients and prescribers complaining of stigma and reduced access to needed opioid analgesics. In response to this and to the availability of new evidence, the CDC published updates to the guideline in 2022 [4]. The updated clinical practice guideline is intended to achieve improved communication between clinicians and patients about the risks and benefits of pain treatment, including opioid therapy for pain; improved safety and effectiveness for pain treatment, resulting in improved function and quality of life for patients experiencing pain; and a reduction in the risks associated with long-term opioid therapy, including opioid use disorder, overdose, and death [4].

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

Each of the 12 recommendations is followed by considerations for implementation. These implementation considerations offer practical insights meant to further inform clinician-patient decision-making for the respective recommendation and are not meant to be rigidly or inflexibly followed. In addition, these five guiding principles should broadly inform implementation across recommendations:

- Acute, subacute, and chronic pain need to be appropriately and effectively treated independent of whether opioids are part of a treatment regimen.
- Recommendations are voluntary and are intended to support, not supplant, individualized, person-centered care. Flexibility to meet the care needs and the clinical circumstances of a specific patient are paramount.
- A multimodal and multidisciplinary approach to pain management attending to the physical health, behavioral health, long-term services and supports, and expected health outcomes and well-being of each person is critical.
- Special attention should be given to avoid misapplying this updated clinical practice guideline beyond its intended use or implementing policies purportedly derived from it that might lead to unintended consequences for patients.
- Clinicians, practices, health systems, and payers should vigilantly attend to health inequities, provide culturally and linguistically appropriate communication, including communication that is accessible to persons with disabilities, and ensure access to an appropriate, affordable, diversified, coordinated, and effective nonpharmacologic and pharmacologic pain management regimen for all persons.

CDC GUIDELINE RECOMMENDATION GRADING SCHEME	
Grade/Level	**Description**
Recommendation Categories	
A	Applies to all persons; most patients should receive the recommended course of action.
B	Individual decision making needed; different choices will be appropriate for different patients. Clinicians help patients arrive at a decision consistent with patient values and preferences and specific clinical situations.
Evidence Type	
1	Randomized clinical trials or overwhelming evidence from observational studies.
2	Randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies.
3	Observational studies or randomized clinical trials with notable limitations.
4	Clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations.

Source: [4] *Table 1*

The following sections are reprinted from the 2022 guideline from the CDC [4].

DETERMINING WHETHER OR NOT TO INITIATE OPIOIDS FOR PAIN

All patients with pain should receive treatment that provides the greatest benefits relative to risks. See Recommendation 1 for determining whether to initiate opioids for acute pain (i.e., with a duration of less than one month) and Recommendation 2 for determining whether or not to initiate opioids for subacute (i.e., with a duration of at least one month and less than three months) or chronic pain (i.e., with a duration of three months or more).

Recommendation 1

Nonopioid therapies are at least as effective as opioids for many common types of acute pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient. Before prescribing opioid therapy for acute pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy (recommendation category: B, evidence type: 3).

Implementation Considerations

Nonopioid therapies are at least as effective as opioids for many common acute pain conditions, including low back pain, neck pain, pain related to other musculoskeletal injuries (e.g., sprains, strains, tendonitis, and bursitis), pain related to minor surgeries typically associated with minimal tissue injury and mild postoperative pain (e.g., simple dental extraction), dental pain, kidney stone pain, and headaches including episodic migraine.

Clinicians should maximize use of nonopioid pharmacologic (e.g., topical or oral nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen) and nonpharmacologic (e.g., ice, heat, elevation, rest, immobilization, or exercise) therapies as appropriate for the specific condition.

Opioid therapy has an important role for acute pain related to severe traumatic injuries (including crush injuries and burns), invasive surgeries typically associated with moderate-to-severe postoperative pain, and other severe acute pain when NSAIDs and other therapies are contraindicated or likely to be ineffective.

Opioids are not first-line therapy for many common acute pain conditions, including low back pain, neck pain, pain related to other musculoskeletal injuries (such as sprains, strains, tendonitis, bursitis), pain related to minor surgeries typically associated with minimal tissue injury and only mild postoperative pain (e.g., dental extraction), dental pain, kidney stone pain, and headaches, including episodic migraine.

When diagnosis and severity of acute pain warrant the use of opioids, clinicians should prescribe immediate-release opioids (see Recommendation 3) at the lowest effective dose (see Recommendation 4) and for no longer than the expected duration of pain severe enough to require opioids (see Recommendation 6).

Clinicians should prescribe and advise opioid use only as needed (e.g., hydrocodone 5 mg/acetaminophen 325 mg, one tablet not more frequently than every 4 hours as needed for moderate-to-severe pain) rather than on a scheduled basis (e.g., one tablet every 4 hours) and encourage and recommend an opioid taper if opioids are taken around the clock for more than a few days (see Recommendation 6).

If patients already receiving opioids long term require additional medication for acute pain, nonopioid medications should be used when possible, and if additional opioids are required (e.g., for superimposed severe acute pain), they should be continued only for the duration of pain severe enough to require additional opioids, returning to the patient's baseline opioid dosage as soon as possible, including a taper to baseline dosage if additional opioids were used around the clock for more than a few days (see Recommendation 6).

Clinicians should ensure that patients are aware of expected benefits of, common and serious risks of, and alternatives to opioids before starting or continuing opioid therapy and should involve patients meaningfully in decisions about whether to start opioid therapy.

Recommendation 2

Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient. Before starting opioid therapy for subacute or chronic pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy, should work with patients to establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks (recommendation category: A, evidence type: 2).

Implementation Considerations

To guide patient-specific selection of therapy, clinicians should evaluate patients and establish or confirm the diagnosis.

Clinicians should recommend appropriate noninvasive, nonpharmacologic approaches to help manage chronic pain, such as exercise (e.g., aerobic, aquatic, resistance exercises) or exercise therapy (a prominent modality in physical therapy) for back pain, fibromyalgia, and hip or knee osteoarthritis; weight loss for knee osteoarthritis; manual therapies for hip osteoarthritis; psychological therapy, spinal manipulation, low-level laser therapy, massage, mindfulness-based stress reduction, yoga, acupuncture, and multidisciplinary rehabilitation for low back pain; mind-body practices (e.g., yoga, tai chi, qigong), massage, and acupuncture for neck pain; cognitive-behavioral therapy [CBT], myofascial release massage, mindfulness practices, tai chi, qigong, acupuncture, and multidisciplinary rehabilitation for fibromyalgia; and spinal manipulation for tension headache.

Low-cost options to integrate exercise include walking in public spaces or use of public recreation facilities for group exercise. Physical therapy can be helpful, particularly for patients who have limited access to safe public spaces or public recreation facilities for exercise or whose pain has not improved with low-intensity physical exercise.

Health insurers and health systems can improve pain management and reduce medication use and associated risks by increasing reimbursement for and access to noninvasive, nonpharmacologic therapies with evidence for effectiveness.

Clinicians should review U.S. Food and Drug Administration (FDA)-approved labeling including boxed warnings and weigh benefits and risks before initiating treatment with any pharmacologic therapy.

When patients affected by osteoarthritis have an insufficient response to nonpharmacologic interventions such as exercise for arthritis pain, topical NSAIDs can be used in patients with pain in a single or few joints near the surface of the skin (e.g., knee). For patients with osteoarthritis pain in multiple joints or incompletely controlled with topical NSAIDs, duloxetine or systemic NSAIDs can be considered.

NSAIDs should be used at the lowest effective dose and shortest duration needed and should be used with caution, particularly in older adults and in patients with cardiovascular comorbidities, chronic renal failure, or previous gastrointestinal bleeding.

When patients with chronic low back pain have had an insufficient response to nonpharmacologic approaches such as exercise, clinicians can consider NSAIDs or duloxetine for patients without contraindications.

Tricyclic, tetracyclic, and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants, selected anticonvulsants (e.g., pregabalin, gabapentin enacarbil, oxcarbazepine), and capsaicin and lidocaine patches can be considered for neuropathic pain.

Duloxetine and pregabalin are FDA-approved for the treatment of diabetic peripheral neuropathy, and pregabalin and gabapentin are FDA-approved for treatment of post-herpetic neuralgia.

In patients with fibromyalgia, tricyclic (amitriptyline) and SNRI antidepressants (duloxetine and milnacipran), NSAIDs (topical diclofenac), and specific anticonvulsants (pregabalin and gabapentin) are used to improve pain, function, and quality of life. Duloxetine, milnacipran, and pregabalin are FDA-approved for the treatment of fibromyalgia. In older adults, decisions to use tricyclic antidepressants should be made judiciously on a case-by-case basis because of risks for confusion and falls.

Patients with co-occurring pain and depression might be especially likely to benefit from antidepressant medication (see Recommendation 8).

Opioids should not be considered first-line or routine therapy for subacute or chronic pain. This does not mean that patients should be required to sequentially fail nonpharmacologic and nonopioid pharmacologic therapy or be required to use any specific treatment before proceeding to opioid therapy. Rather, expected benefits specific to the clinical context should be weighed against risks before initiating therapy. In some clinical contexts (e.g., serious illness in a patient with poor prognosis for return to previous level of function, contraindications to other therapies, and clinician and patient agreement that

the overriding goal is patient comfort), opioids might be appropriate regardless of previous therapies used. In other situations, (e.g., headache or fibromyalgia), expected benefits of initiating opioids are unlikely to outweigh risks regardless of previous nonpharmacologic and nonopioid pharmacologic therapies used.

Opioid therapy should not be initiated without consideration by the clinician and patient of an exit strategy to be used if opioid therapy is unsuccessful.

Before opioid therapy is initiated for subacute or chronic pain, clinicians should determine jointly with patients how functional benefit will be evaluated and establish specific, measurable treatment goals.

For patients with subacute pain who started opioid therapy for acute pain and have been treated with opioid therapy for ≥30 days, clinicians should ensure that potentially reversible causes of chronic pain are addressed and that opioid prescribing for acute pain does not unintentionally become long-term opioid therapy simply because medications are continued without reassessment. Continuation of opioid therapy at this point might represent initiation of long-term opioid therapy, which should occur only as an intentional decision that benefits are likely to outweigh risks after informed discussion between the clinician and patient and as part of a comprehensive pain management approach.

Clinicians seeing new patients already receiving opioids should establish treatment goals, including functional goals, for continued opioid therapy. Clinicians should avoid rapid tapering or abrupt discontinuation of opioids (see Recommendation 5).

Patient education and discussion before starting opioid therapy are critical so that patient preferences and values can be understood and used to inform clinical decisions.

Clinicians should review available low-cost options for pain management for all patients, and particularly for patients who have low incomes, do not have health insurance, or have inadequate insurance.

Clinicians should ensure that patients are aware of expected benefits of, common and serious risks of, and alternatives to opioids before starting or continuing opioid therapy and should involve patients in decisions about whether to start opioid therapy.

OPIOID SELECTION AND DOSAGE

Recommendation 3

When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release and long-acting (ER/LA) opioids (recommendation category: A, evidence type: 4).

Implementation Considerations

Clinicians should not treat acute pain with ER/LA opioids or initiate opioid treatment for subacute or chronic pain with ER/LA opioids, and clinicians should not prescribe ER/LA opioids for intermittent or as needed use.

ER/LA opioids should be reserved for severe, continuous pain. The FDA has noted that some ER/LA opioids should be considered only for patients who have received certain dosages of opioids of immediate-release opioids daily for at least 1 week.

When changing to an ER/LA opioid for a patient previously receiving a different immediate-release opioid, clinicians should consult product labeling and reduce total daily dosage to account for incomplete opioid cross-tolerance.

Clinicians should use additional caution with ER/LA opioids and consider a longer dosing interval when prescribing to patients with renal or hepatic dysfunction because decreased clearance of medications among these patients can lead to accumulation of drugs to toxic levels and persistence in the body for longer durations.

Methadone should not be the first choice for an ER/LA opioid. Only clinicians who are familiar with methadone's unique risk profile and who are prepared to educate and closely monitor their patients, including assessing risk for QT prolongation and considering electrocardiographic monitoring, should consider prescribing methadone for pain.

Only clinicians who are familiar with the dosing and absorption properties of the ER/LA opioid transdermal fentanyl and are prepared to educate their patients about its use should consider prescribing it.

Recommendation 4

When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest effective dosage. If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage, should carefully evaluate individual benefits and risks when considering increasing dosage, and should avoid increasing dosage above levels likely to yield diminishing returns in benefits relative to risks to patients (recommendation category: A, evidence type: 3).

Implementation Considerations

The recommendations related to opioid dosages are not intended to be used as an inflexible, rigid standard of care; rather, they are intended to be guideposts to help inform clinician-patient decision-making. Risks of opioid use, including risk for overdose and overdose death, increase continuously with dosage, and there is no single dosage threshold below which risks are eliminated. Therefore, the recommendation language emphasizes that clinicians should avoid increasing dosage above levels likely to yield diminishing returns in benefits relative to risks to patients rather than emphasizing a single specific numeric threshold. Further, these recommendations apply specifically to starting opioids or to increasing opioid dosages, and a different set of benefits and risks applies to reducing opioid dosages (see Recommendation 5).

When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest effective dosage.

For patients not already taking opioids, the lowest effective dose can be determined using product labeling as a starting point with calibration as needed based on the severity of pain and other clinical factors such as renal or hepatic insufficiency (see Recommendation 8).

The lowest starting dose for opioid-naïve patients is often equivalent to a single dose of approximately 5–10 MME or a daily dosage of 20–30 MME/day.

If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage and should generally avoid dosage increases when possible.

Many patients do not experience benefit in pain or function from increasing opioid dosages to ≥50 MME/day but are exposed to progressive increases in risk as dosage increases. Therefore, before increasing total opioid dosage to ≥50 MME/day, clinicians should pause and carefully reassess evidence of individual benefits and risks. If a decision is made to increase dosage, clinicians should use caution and increase dosage by the smallest practical amount. The recommendations related to opioid dosages are not intended to be used as an inflexible, rigid standard of care; rather, they are intended to be guideposts to help inform clinician-patient decision-making.

Additional dosage increases beyond 50 MME/day are progressively more likely to yield diminishing returns in benefits for pain and function relative to risks to patients as dosage increases further. Clinicians should carefully evaluate a decision to further increase dosage based on the basis of individualized assessment of benefits and risks and weighing factors such as diagnosis, incremental benefits for pain and function relative to risks with previous dosage increases, other treatments and effectiveness, and patient values and preferences.

Again, the recommendations related to opioid dosages are not intended to be used as an inflexible, rigid standard of care; rather, they are intended to be guideposts to help inform clinician-patient decision making.

Recommendation 5

For patients already receiving opioid therapy, clinicians should carefully weigh benefits and risks and exercise care when changing opioid dosage. If benefits outweigh risks of continued opioid therapy, clinicians should work closely with patients to optimize nonopioid therapies while continuing opioid therapy. If benefits do not outweigh risks of continued opioid therapy, clinicians should optimize other therapies and work closely with patients to gradually taper to lower dosages or, if warranted based on the individual circumstances of the patient, appropriately taper and discontinue opioids. Unless there are indications of a life-threatening issue, such as warning signs of impending overdose (e.g., confusion, sedation, slurred speech), opioid therapy should not be discontinued abruptly, and clinicians should not rapidly reduce opioid dosages from higher dosages (recommendation category: B, evidence type: 4).

interactive activity

View the CDC's video Tapering Opioids for Chronic Pain at https://youtu.be/89UXlpijYyE. This short video describes when and how clinicians should initiate opioid tapering and outlines ways to support patients through the process.

Implementation Considerations

Clinicians should carefully weigh both the benefits and risks of continuing opioid medications and the benefits and risks of tapering opioids. If benefits outweigh risks of continued opioid therapy, clinicians should work closely with patients to optimize nonopioid therapies while continuing opioid therapy.

When benefits (including avoiding risks of tapering) do not outweigh risks of continued opioid therapy, clinicians should optimize other therapies and work closely with patients to gradually taper to a reduced opioid dosage or, if warranted based on the individual clinical circumstances of the patient, appropriately taper and discontinue opioid therapy.

In situations where benefits and risks of continuing opioids are considered to be close or unclear, shared decision-making with patients is particularly important.

At times, clinicians and patients might not be able to agree on whether or not tapering is necessary. When patients and clinicians are unable to arrive at a consensus on the assessment of benefits and risks, clinicians should acknowledge this discordance, express empathy, and seek to implement treatment changes in a patient-centered manner while avoiding patient abandonment.

Patient agreement and interest in tapering is likely to be a key component of successful tapers.

For patients agreeing to taper to lower opioid dosages and for those remaining on higher opioid dosages, clinicians should establish goals with the patient for continued opioid therapy (see Recommendations 2 and 7) and maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 2).

Clinicians should collaborate with the patient on the tapering plan, including patients in decisions such as how quickly tapering will occur and when pauses in the taper may be warranted.

Clinicians should follow up frequently (at least monthly) with patients engaging in opioid tapering. Team members (e.g., nurses, pharmacists, behavioral health professionals) can support the clinician and patient during the ongoing taper process through telephone contact, telehealth visits, or face-to-face visits.

When opioids are reduced or discontinued, a taper slow enough to minimize symptoms and signs of opioid withdrawal (e.g., anxiety, insomnia, abdominal pain, vomiting, diarrhea, diaphoresis, mydriasis, tremor, tachycardia, or piloerection) should be used.

Longer duration of previous opioid therapy might require a longer taper. For patients who have taken opioids long-term (e.g., for ≥1 year), tapers can be completed over several months to years depending on the opioid dosage and should be individualized based on patient goals and concerns.

When patients have been taking opioids for longer durations (e.g., for ≥1 year), tapers of 10% per month or slower are likely to be better tolerated than more rapid tapers.

For patients struggling to tolerate a taper, clinicians should maximize nonopioid treatments for pain and should address behavioral distress. Clinically significant opioid withdrawal symptoms can signal the need to further slow the taper rate.

At times, tapers might have to be paused and restarted again when the patient is ready and might have to be slowed as patients reach low dosages.

Before reversing a taper, clinicians should carefully assess and discuss with the patient the benefits and risks of increasing opioid dosage.

Goals of the taper may vary (e.g., some patients might achieve discontinuation; others might attain a reduced dosage). If the clinician has determined with the patient that the ultimate goal of tapering is discontinuing opioids, after the smallest available dose is reached the interval between doses can be extended and opioids can be stopped when taken less frequently than once a day.

Clinicians should access appropriate expertise if considering tapering opioids during pregnancy because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal.

Clinicians should advise patients of an increased risk for overdose on abrupt return to a previously prescribed higher dose, because of loss of opioid tolerance, provide opioid overdose education, and offer naloxone.

Clinicians should remain alert to signs of and screen for anxiety, depression, and opioid misuse or opioid use disorder (see Recommendations 8 and 12) that might be revealed by an opioid taper and provide treatment or arrange for management of these comorbidities.

Clinicians should closely monitor patients who are unable to taper and who continue on high-dose or otherwise high-risk opioid regimens (e.g., opioids prescribed concurrently with benzodiazepines) and should work with patients to mitigate overdose risk (e.g., by providing overdose education and naloxone—see Recommendation 8).

Clinicians can use periodic and strategic motivational questions and statements to encourage movement toward appropriate therapeutic changes and functional goals.

Clinicians have a responsibility to provide or arrange for coordinated management of patients' pain and opioid-related problems, including opioid use disorder.

Payers, health systems, and state medical boards should not use this clinical practice guideline to set rigid standards or performance incentives related to dose or duration of opioid therapy; should ensure that policies based on cautionary dosage thresholds do not result in rapid tapers or abrupt discontinuation of opioids; and should ensure that policies do not penalize clinicians for accepting new patients who are using prescribed opioids for chronic pain, including those receiving high dosages of opioids, or for refraining from rapidly tapering patients prescribed long-term opioid medications.

Although Recommendation 5 specifically refers to patients using long-term opioid therapy for subacute or chronic pain, many of the principles in these implementation considerations and supporting rationale, including communication with patients, pain management and behavioral support, and slower taper rates, are also relevant when discontinuing opioids in patients who have received them for shorter durations (see also Recommendations 6 and 7).

OPIOID DURATION AND FOLLOW-UP

Recommendation 6

When opioids are needed for acute pain, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids (recommendation category: A, evidence type: 4).

Implementation Considerations

Nontraumatic, nonsurgical acute pain can often be managed without opioids (see Recommendation 1).

Opioids are sometimes needed for treatment of acute pain (see Recommendation 1). When the diagnosis and severity of acute pain warrant use of opioids, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. For many common causes of nontraumatic, nonsurgical pain, when opioids are needed, a few days or less are often sufficient, and shorter courses can minimize the need to taper opioids to prevent withdrawal symptoms at the end of a course of opioids. However, durations should be individualized to the patients' clinical circumstances.

Clinicians should generally avoid prescribing additional opioids to patients "just in case" pain continues longer than expected.

For postoperative pain related to major surgery, procedure-specific opioid prescribing recommendations are available with ranges for amounts of opioids needed (on the basis of actual use and refills and on consensus).

To minimize unintended effects on patients, clinicians, practices, and health systems should have mechanisms in place for the subset of patients who experience severe acute pain that continues longer than the expected duration. These mechanisms should allow for timely re-evaluation to confirm or revise the initial diagnosis and to adjust management accordingly. Clinicians, practices, and health systems can help minimize disparities in access to and affordability of care and refills by ensuring all patients can obtain and afford additional evaluation and treatment, as needed.

Longer durations of opioid therapy are more likely to be needed when the mechanism of injury is expected to result in prolonged severe pain (e.g., severe traumatic injuries).

Patients should be evaluated at least every 2 weeks if they continue to receive opioids for acute pain.

If opioids are continued for ≥1 month, clinicians should ensure that potentially reversible causes of chronic pain are addressed and that opioid prescribing for acute pain does not unintentionally become long-term opioid therapy simply because medications are continued without reassessment. Continuation of opioid therapy at this point might represent initiation of long-term opioid therapy, which should occur only as an intentional decision that benefits are likely to outweigh risks after discussion between the clinician and patient and as part of a comprehensive pain management approach. Clinicians should refer to recommendations on subacute and chronic pain for initiation (Recommendation 2), follow-up (Recommendation 7), and tapering (Recommendation 5) of ongoing opioid therapy.

If patients already receiving long-term opioid therapy require additional opioids for superimposed severe acute pain (e.g., major surgery), opioids should be continued only for the duration of pain severe enough to require additional opioids, returning to the patient's baseline opioid dosage as soon as possible, including a taper to baseline dosage if additional opioids were used around the clock for more than a few days.

If opioids are used continuously (around the clock) for more than a few days for acute pain, clinicians should prescribe a brief taper to minimize withdrawal symptoms on discontinuation of opioids.

If a taper is needed, taper durations might need to be adjusted depending on the duration of the initial opioid prescription (see supporting rationale for this recommendation for additional details).

Tapering plans should be discussed with the patient prior to hospital discharge and with clinicians coordinating the patient's care as an outpatient. (See Recommendation 5 for tapering considerations when patients have taken opioids continuously for longer than one month.)

Recommendation 7

Clinicians should evaluate benefits and risks with patients within one to four weeks of starting opioid therapy for subacute or chronic pain or of dosage escalation. Clinicians should regularly re-evaluate benefits and risks of continued opioid therapy with patients (recommendation category: A, evidence type: 4).

Implementation Considerations

In addition to evaluating benefits and risks of opioids before starting opioid therapy (see Recommendation 2), clinicians should evaluate patients to assess benefits and risks of opioids within 1 to 4 weeks of starting long-term opioid therapy or of dosage escalation.

Clinicians should consider follow-up intervals within the lower end of this range when ER/LA opioids are started or increased, given increased risk for overdose within the first 2 weeks of treatment, or when total daily opioid dosage is ≥50 MME/day. (Overdose risk is doubled across multiple studies for dosages of 50 to <100 MME/day relative to <20 MME/day. See Recommendation 4.)

Shorter follow-up intervals (every two to three days for the first week) should be strongly considered when starting or increasing the dosage of methadone, given the variable half-life of this drug (see Recommendation 3) and the potential for drug accumulation during initiation and during upward titration of dosage.

An initial follow-up interval closer to 4 weeks can be considered when starting immediate-release opioids at a dosage of <50 MME/day.

Clinicians should follow up with and evaluate patients with subacute pain who started opioid therapy for acute pain and have been treated with opioid therapy for 30 days to reassess the patient's pain, function, and treatment course; ensure that potentially reversible causes of chronic pain are addressed; and prevent unintentional initiation of long-term opioid therapy. Continuation of opioid therapy at this point might represent initiation of long-term opioid therapy, which should occur only as an intentional decision that benefits are likely to outweigh risks after discussion between the clinician and patient and as part of a comprehensive pain management approach (see Recommendation 2).

Clinicians should regularly reassess all patients receiving long-term opioid therapy, including patients who are new to the clinician but on long-term opioid therapy, with a suggested interval of every three months or more frequently for most patients.

Clinicians seeing new patients already receiving opioids should establish treatment goals, including functional goals, for continued opioid therapy (see Recommendation 2).

Clinicians should re-evaluate patients who are at higher risk for opioid use disorder or overdose (e.g., patients with depression or other mental health conditions, a history of substance use

disorder, a history of overdose, taking ≥50 MME/day, or taking other central nervous system depressants with opioids) more frequently than every 3 months. Clinicians should regularly screen all patients for these conditions, which can change during the course of treatment (see Recommendation 8).

Clinicians, practices, and health systems can help minimize unintended effects on patients by ensuring all patients can access and afford follow-up evaluation.

In practice contexts where virtual visits are part of standard care (e.g., in remote areas where distance or other context makes follow-up visits challenging), or for patients for whom in-person follow-up visits are challenging (e.g., frail patients), follow-up assessments that allow the clinician to communicate with and observe the patient through telehealth modalities may be conducted.

At follow-up, clinicians should review patient perspectives and goals, determine whether opioids continue to meet treatment goals, including sustained improvement in pain and function and determine whether the patient has experienced common or serious adverse events or early warning signs of serious adverse events or has signs of opioid use disorder.

Clinicians should ensure that treatment for depression, anxiety, or other psychological comorbidities is optimized.

Clinicians should ask patients about their preferences for continuing opioids, considering their effects on pain and function relative to any adverse effects experienced. If risks outweigh benefits of continued opioid therapy (e.g., if patients do not experience meaningful, sustained improvements in pain and function compared with prior to initiation of opioid therapy; if patients are taking higher-risk regimens [e.g., dosages of ≥50 MME/day or opioids combined with benzodiazepines] without evidence of benefit; if patients believe benefits no longer outweigh risks; if patients request dosage reduction or discontinuation; or if patients experience overdose or other serious adverse events), clinicians should work with patients to taper and reduce opioid dosage or taper and discontinue opioids when possible, using principles from Recommendation 5.

Clinicians should maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 2).

ASSESSING RISK AND ADDRESSING HARMS OF OPIOID USE

Recommendation 8

Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss risk with patients. Clinicians should work with patients to incorporate into the management plan strategies to mitigate risk, including offering naloxone (recommendation category: A, evidence type: 4).

Implementation Considerations

Clinicians should ask patients about their drug and alcohol use and use validated tools or consult with behavioral specialists to screen for and assess mental health and substance use disorders.

When considering initiating long-term opioid therapy, clinicians should ensure that treatment for depression and other mental health conditions is optimized, consulting with behavioral health specialists when needed.

Clinicians should offer naloxone when prescribing opioids, particularly to patients at increased risk for overdose, including patients with a history of overdose, patients with a history of substance use disorder, patients with sleep-disordered breathing, patients taking higher dosages of opioids (e.g., ≥50 MME/day), patients taking benzodiazepines with opioids (see Recommendation 11), and patients at risk for returning to a high dose to which they have lost tolerance (e.g., patients undergoing tapering or recently released from prison).

Practices should educate patients on overdose prevention and naloxone use and offer to provide education to members of their households.

Naloxone co-prescribing can be facilitated by clinics or practices with resources to provide naloxone training and by collaborative practice models with pharmacists or through statewide protocols or standing orders for naloxone at pharmacies.

Resources for prescribing naloxone in primary care and emergency department settings can be found through Prescribe to Prevent at http://prescribetoprevent.org; additional resources are at https://samhsa.gov.

In part because of concerns about cost of naloxone and access for some patients and reports that purchasing of naloxone has in some cases been required to fill opioid prescriptions, including for patients without a way to afford naloxone, this recommendation specifies that naloxone should be offered to patients. To that end, clinicians, health systems, and payers can work to ensure patients can obtain naloxone, a potentially lifesaving treatment.

Clinicians should avoid prescribing opioids to patients with moderate or severe sleep-disordered breathing when possible to minimize risk for respiratory depression.

When making decisions about whether to initiate opioid therapy for pain during pregnancy, clinicians and patients together should carefully weigh benefits and risks. For pregnant people already receiving opioids, clinicians should access appropriate expertise if tapering is being considered because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal (see Recommendation 5).

For pregnant people with opioid use disorder, medication for opioid use disorder (buprenorphine or methadone) is the recommended therapy and should be offered as early as possible in pregnancy to prevent harms to both the patient and the fetus (see Recommendation 12).

Clinicians should use additional caution and increased monitoring (see Recommendation 7) to minimize risks of opioids prescribed for patients with renal or hepatic insufficiency and for patients aged ≥65 years. Clinicians should implement interventions to mitigate common risks of opioid therapy among older adults, such as exercise or bowel regimens to prevent constipation, risk assessment for falls, and patient monitoring for cognitive impairment.

For patients with jobs that involve potentially hazardous tasks and who are receiving opioids or other medications that can negatively affect sleep, cognition, balance, or coordination, clinicians should assess patients' abilities to safely perform the potentially hazardous tasks (e.g., driving, use of heavy equipment, climbing ladders, working at heights or around moving machinery, or working with high-voltage equipment).

Clinicians should use prescription drug monitoring program (PDMP) data (see Recommendation 9) and toxicology screening (see Recommendation 10) as appropriate to assess for concurrent substance use that might place patients at higher risk for opioid use disorder and overdose.

Clinicians should provide specific counseling on increased risks for overdose when opioids are combined with other drugs or alcohol (see Recommendation 2) and ensure that patients are provided or receive effective treatment for substance use disorders when needed (see Recommendation 12).

Although substance use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. (See Recommendation 12 Pain Management for Patients with Opioid Use Disorder for additional considerations specific to these patients.)

If clinicians consider opioid therapy for chronic pain for patients with substance use disorder, they should discuss increased risks for opioid use disorder and overdose with patients, carefully consider whether benefits of opioids outweigh increased risks, and incorporate strategies to mitigate risk into the management plan, such as offering naloxone and increasing frequency of monitoring (see Recommendation 7).

If patients experience nonfatal opioid overdose, clinicians should evaluate for opioid use disorder and treat or arrange treatment if needed. Clinicians should work with patients to reduce opioid dosage and to discontinue opioids when indicated (see Recommendation 5) and should ensure continued close monitoring and support for patients prescribed or not prescribed opioids. If clinicians continue opioid therapy in patients with prior opioid overdose, they should discuss increased risks for overdose with patients, carefully consider whether benefits of opioids outweigh substantial risks, and incorporate strategies to mitigate risk into the management plan, such as considering offering naloxone and increasing frequency of monitoring (see Recommendation 7).

Recommendation 9

When prescribing initial opioid therapy for acute, subacute, or chronic pain, and periodically during opioid therapy for chronic pain, clinicians should review the patient's history of controlled substance prescriptions using state PDMP data to determine whether the patient is receiving opioid dosages or combinations that put the patient at high risk for overdose (recommendation category: B, evidence type: 4).

Implementation Considerations

Ideally, PDMP data should be reviewed before every opioid prescription for acute, subacute, or chronic pain. This practice is recommended in all jurisdictions where PDMP availability and access policies, as well as clinical practice settings, make it practicable (e.g., clinician and delegate access permitted).

At a minimum, during long-term opioid therapy, PDMP data should be reviewed before an initial opioid prescription and then every three months or more frequently. Recommendation category B acknowledges variation in PDMP availability and circumstances. However, because PDMP information can be most helpful when results are unexpected, and to minimize bias in application, clinicians should apply this recommendation when feasible to all patients rather than differentially based on assumptions about what they will learn about specific patients.

Clinicians should use specific PDMP information about medications prescribed to their patient in the context of other clinical information, including their patient's history, physical findings, and other relevant testing, to help them communicate with and protect their patient.

Clinicians should review PDMP data specifically for prescription opioids and other controlled medications patients have received from additional prescribers to determine whether a patient is receiving total opioid dosages or combinations (e.g., opioids combined with benzodiazepines) that put the patient at risk for overdose.

PDMP-generated risk scores have not been validated against clinical outcomes such as overdose and should not take the place of clinical judgment. Clinicians should not dismiss patients from their practice on the basis of PDMP information. Doing so can adversely affect patient safety and could result in missed opportunities to provide potentially lifesaving information (e.g., about risks of prescription opioids and about overdose prevention) and interventions (e.g., safer prescriptions, nonopioid pain treatment [see Recommendations 1 and 2], naloxone [see Recommendation 8], and effective treatment for substance use disorder [see Recommendations 8 and 12]).

Clinicians should take actions to improve patient safety:

- Discuss information from the PDMP with their patient and confirm that their patient is aware of any additional prescriptions. Because clinicians often work as part of teams, prescriptions might appropriately be written by more than one clinician coordinating the patient's care. Occasionally, PDMP information can be incorrect (e.g., if the wrong name or birthdate has been entered, the patient uses a nickname or maiden name, or another person has used the patient's identity to obtain prescriptions).
- Discuss safety concerns, including increased risk for respiratory depression and overdose, with patients found to be receiving overlapping prescription opioids from multiple clinicians who are not coordinating the patient's care or patients who are receiving medications that increase risk when combined with opioids (e.g., benzodiazepines; see Recommendation 11) and offer naloxone (see Recommendation 8).
- Use particular caution when prescribing opioid pain medication and benzodiazepines concurrently, understanding that some patient circumstances warrant prescribing of these medications concomitantly. Clinicians should communicate with others managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care (see Recommendation 11).
- Consider the total MME/day for concurrent opioid prescriptions to help assess the patient's overdose risk (see Recommendation 4). Buprenorphine should not be counted in the total MME/day in calculations given its partial agonist properties at opioid receptors that confer a ceiling effect on respiratory depression. If patients are found to be receiving total daily dosages of opioids that put them at risk for overdose, discuss safety concerns with the patient, consider in collaboration with the patient whether or not benefits of tapering outweigh risks of tapering (see Recommendation 5), and offer naloxone (see Recommendation 8).
- Discuss safety concerns with other clinicians who are prescribing controlled substances for their patient. Ideally, clinicians should first discuss concerns with their patient and inform him or her that they plan to coordinate care with the patient's other clinicians to improve the patient's safety.
- Screen for substance use and discuss concerns with their patient in a nonjudgmental manner (see Recommendations 8 and 12).
- When diverting (sharing or selling prescription opioids and not taking them) might be likely, consider toxicology testing to assist in determining whether prescription opioids can be discontinued without causing withdrawal (see Recommendations 5 and 10). A negative toxicology test for prescribed opioids might indicate the patient is not taking prescribed opioids, although clinicians should consider other possible reasons for this test result, such as false negative results or misinterpretation of results (see Recommendation 10).

Recommendation 10

When prescribing opioids for subacute or chronic pain, clinicians should consider the benefits and risks of toxicology testing to assess for prescribed medications as well as other prescribed and non-prescribed controlled substances (recommendation category: B, evidence type: 4).

Implementation Considerations

Toxicology testing should not be used in a punitive manner but should be used in the context of other clinical information to inform and improve patient care.

Clinicians should not dismiss patients from care based on a toxicology test result. Dismissal could have adverse consequences for patient safety, potentially including the patient obtaining opioids or other drugs from alternative sources and the clinician missing opportunities to facilitate treatment for substance use disorder.

Prior to starting opioids and periodically (at least annually) during opioid therapy, clinicians should consider the benefits and risks of toxicology testing to assess for prescribed opioids as well as other prescription and nonprescription controlled substances that increase risk for overdose when combined with opioids, including nonprescribed and illicit opioids and benzodiazepines.

Clinicians, practices, and health systems should aim to minimize bias in testing and should not apply this recommendation differentially based on assumptions about patients.

Predicting risk is challenging, and currently available tools do not allow clinicians to reliably identify patients who are at low risk for substance use or substance use disorder. Clinicians should consider toxicology screening results as potentially useful data, in the context of other clinical information, for all patients, and consider toxicology screening whenever its potential limitations can be addressed.

Clinicians should explain to patients that toxicology testing will not be used to dismiss patients from care and is intended to improve their safety.

Clinicians should explain expected results (e.g., presence of prescribed medication and absence of drugs, including non-prescribed controlled substances, not reported by the patient) and ask patients in a nonjudgmental manner about use of prescribed and other drugs and whether there might be unexpected results.

Limited toxicology screening can be performed with a relatively inexpensive presumptive immunoassay panel that tests for opiates as a class, benzodiazepines as a class, and several non-

prescribed substances. Toxicology screening for a class of drugs might not detect all drugs in that class. For example, fentanyl testing is not included in widely used toxicology assays that screen for opiates as a class.

Clinicians should be familiar with the drugs included in toxicology screening panels used in their practice and should understand how to interpret results for these drugs. For example, a positive "opiates" immunoassay detects morphine, which might reflect patient use of morphine, codeine, or heroin, but does not detect synthetic opioids and might not detect semisynthetic opioids. In some cases, positive results for specific opioids might reflect metabolites from opioids the patient is taking and might not mean the patient is taking the specific opioid that resulted in the positive test. Confirmatory testing should be used when:

- Toxicology results will inform decisions with major clinical or nonclinical implications for the patient
- A need exists to detect specific opioids or other drugs within a class, such as those that are being prescribed, or those that cannot be identified on standard immunoassays
- A need exists to confirm unexpected screening toxicology test results

Restricting confirmatory testing to situations and substances for which results can reasonably be expected to affect patient management can reduce costs of toxicology testing.

Clinicians might want to discuss unexpected results with the local laboratory or toxicologist and should discuss unexpected results with the patient. Clinicians should discuss unexpected results with patients in a nonjudgmental manner, avoiding use of potentially stigmatizing language (e.g., avoid describing a specimen as testing "clean" or "dirty").

Discussion with patients prior to specific confirmatory testing can sometimes yield a candid explanation of why a particular substance is present or absent and remove the need for confirmatory testing during that visit. For example, a patient might explain that the test is negative for prescribed opioids because they felt opioids were no longer helping and discontinued them. If unexpected results from toxicology screening are not explained, a confirmatory test on the same sample using a method selective enough to differentiate specific opioids and metabolites (e.g., gas or liquid chromatography/mass spectrometry) might be warranted.

Clinicians should use unexpected results to improve patient safety (e.g., optimize pain management strategy [see Recommendation 2], carefully weigh benefits and risks of reducing or continuing opioid dosage [see Recommendation 5], re-evaluate more frequently [see Recommendation 7], offer naloxone [see Recommendation 8], and offer treatment or refer the patient treatment with medications for opioid use disorder [see Recommendation 12], all as appropriate).

Recommendation 11

Clinicians should use particular caution when prescribing opioid pain medication and benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants (recommendation category: B, evidence type: 3).

Implementation Considerations

Although in some circumstances it might be appropriate to prescribe opioids to a patient who is also prescribed benzodiazepines (e.g., severe acute pain in a patient taking long-term, stable low-dose benzodiazepine therapy), clinicians should use particular caution when prescribing opioid pain medication and benzodiazepines concurrently. In addition, clinicians should consider whether benefits outweigh risks of concurrent use of opioids with other central nervous system depressants (e.g., muscle relaxants, non-benzodiazepine sedative hypnotics, potentially sedating anticonvulsant medications such as gabapentin and pregabalin).

Buprenorphine or methadone for opioid use disorder should not be withheld from patients taking benzodiazepines or other medications that depress the central nervous system.

Clinicians should check the PDMP for concurrent controlled medications prescribed by other clinicians (see Recommendation 9) and should consider involving pharmacists as part of the management team when opioids are co-prescribed with other central nervous system depressants.

In patients receiving opioids and benzodiazepines long-term, clinicians should carefully weigh the benefits and risks of continuing therapy with opioids and benzodiazepines and discuss with patients and other members of the patient's care team.

Risks of concurrent opioid and benzodiazepine use are likely to be greater with unpredictable use of either medication, with use of higher-dosage opioids and higher-dosage benzodiazepines in combination, or with use with other substances including alcohol (compared with long-term stable use of lower-dosage opioids and lower-dosage benzodiazepines without other substances).

In specific situations, benzodiazepines can be beneficial, and stopping benzodiazepines can be destabilizing.

If risks are determined to outweigh benefits of continuing opioid and benzodiazepine therapy at current dosages and a decision is made to taper, it might be safer and more practical to taper opioids first. There can be greater risks of benzodiazepine withdrawal relative to opioid withdrawal, and tapering opioids can be associated with anxiety (see Recommendation 5).

Clinicians should taper benzodiazepines gradually prior to discontinuation because abrupt withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and, rarely, death. The rate of tapering should be individualized.

If benzodiazepines prescribed for anxiety are tapered or discontinued, or if patients receiving opioids require treatment for anxiety, evidence-based psychotherapies (e.g., CBT) and/or specific antidepressants or other nonbenzodiazepine medications, or both, approved for anxiety should be offered.

Clinicians should communicate with other clinicians managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care.

Recommendation 12

Clinicians should offer or arrange treatment evidence-based medications to treat patients with opioid use disorder. Detoxification on its own, without medications for opioid use disorder, is not recommended for opioid use disorder because of increased risks for resuming drug use, overdose, and overdose death (recommendation category: A, evidence type: 1).

Implementation Considerations

Although stigma can reduce the willingness of individuals with opioid use disorder to seek treatment, opioid use disorder is a chronic, treatable disease from which people can recover and continue to lead healthy lives.

If clinicians suspect opioid use disorder, they should discuss their concern with their patient in a nonjudgmental manner and provide an opportunity for the patient to disclose related concerns or problems.

Clinicians should assess for the presence of opioid use disorder using criteria from the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*.

For patients meeting criteria for opioid use disorder, particularly if moderate or severe, clinicians should offer or arrange for patients to receive evidence-based treatment with medications for opioid use disorder.

Clinicians should not dismiss patients from their practice because of opioid use disorder because this can adversely affect patient safety.

Medication treatment of opioid use disorder has been associated with reduced risk for overdose and overall deaths. Identification of opioid use disorder represents an opportunity for a clinician to initiate potentially life-saving interventions, and should the clinician collaborate with the patient regarding their safety to increase the likelihood of successful treatment.

For pregnant persons with opioid use disorder, medication for opioid use disorder (buprenorphine or methadone) is the recommended therapy and should be offered as early as possible in pregnancy to prevent harms to both the patient and the fetus.

Clinicians unable to provide treatment themselves should arrange for patients with opioid use disorder to receive care from a substance use disorder treatment specialist, such as an office-based buprenorphine or naltrexone treatment provider, or from an opioid treatment program certified by Substance Abuse and Mental Health Services Administration to provide methadone or buprenorphine for patients with opioid use disorder.

All clinicians, and particularly clinicians prescribing opioids in communities without sufficient treatment capacity for opioid use disorder, should obtain a waiver to prescribe buprenorphine for opioid use disorder.

Clinicians prescribing opioids should identify treatment resources for opioid use disorder in the community, establish a network of referral options that span the levels of care that patients might need to enable rapid collaboration and referral, when needed, and work together to ensure sufficient treatment capacity for opioid use disorder at the practice level.

Although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and opioid use disorder require ongoing pain management that maximizes benefits relative to risks.

Management of Opioid Misuse that Does Not Meet Criteria for Opioid Use Disorder

Clinicians can have challenges distinguishing between opioid misuse behaviors without opioid use disorder and mild or moderate opioid use disorder. For patients with opioid misuse that does not meet criteria for opioid use disorder (e.g., taking opioids in larger amounts than intended without meeting other criteria for opioid use disorder), clinicians should reassess the patient's pain, ensure that therapies for pain management have been optimized (see Recommendation 2), discuss with patients, and carefully weigh benefits and risks of continuing opioids at the current dosage (see Recommendation 5). For patients who choose to but are unable to taper, clinicians may reassess for opioid use disorder and offer buprenorphine treatment or refer for buprenorphine or methadone treatment if criteria for opioid use disorder are met. Even without a diagnosis of opioid use disorder, transitioning to buprenorphine for pain can also be considered given reduced overdose risk with buprenorphine compared with risk associated with full agonist opioids (see Recommendation 5).

Pain Management for Patients with Opioid Use Disorder

Although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. Clinicians should use nonpharmacologic and nonopioid pharmacologic pain treatments as appropriate (see Recommendations 1 and 2) to provide optimal pain management [49]. For patients with pain who have an active opioid use disorder but are not in treatment, clinicians should consider buprenorphine or methadone treatment for opioid use disorder, which can also help with concurrent management of pain [49]. For patients who are treated with buprenorphine

for opioid use disorder and experience acute pain, clinicians can consider temporarily increasing the buprenorphine dosing frequency (e.g., to twice a day) to help manage pain, given the duration of effects of buprenorphine is shorter for pain than for suppression of withdrawal [49; 50]. For severe acute pain (e.g., from trauma or unplanned major surgery) in patients receiving buprenorphine for opioid use disorder, clinicians can consider additional as-needed doses of buprenorphine. In supervised settings, adding a short-acting full agonist opioid to the patient's regular dosage of buprenorphine can be considered without discontinuing the patient's regular buprenorphine dosage; however, if a decision is made to discontinue buprenorphine to allow for more mu-opioid receptor availability, patients should be monitored closely because high doses of a full agonist opioid might be required, potentially leading to oversedation and respiratory depression as buprenorphine's partial agonist effect lessens. For patients receiving naltrexone for opioid use disorder, short-term use of higher-potency nonopioid analgesics (e.g., NSAIDs) can be considered to manage severe acute pain. Patients receiving methadone for opioid use disorder who require additional opioids as treatment for severe acute pain management should be carefully monitored, and when feasible should optimally be treated by a clinician experienced in the treatment of pain in consultation with their opioid treatment program. [49]. The American Society of Addiction Medicine National Practice Guideline for the Treatment of Opioid Use Disorder (2020 Focused Update) provides additional recommendations for the management of patients receiving medications for opioid use disorder who have planned surgeries for which nonopioid therapies are not anticipated to provide sufficient pain relief [49].

RESPONSE TO THE CDC'S OPIOID PRESCRIBING GUIDELINE UPDATE

It is important to note that the CDC's guidelines are voluntary, and the changes may not result in changes to state laws and rules established to restrict opioid prescribing and help curb opioid misuse following publication of the 2016 guideline. The 2022 guideline emphasizes prescriber decision-making and access to necessary opioid analgesics to address unrelenting pain. The guideline states that some policies have extended even beyond the 2016 recommendations, contributing to patient harm, including untreated and undertreated pain, serious withdrawal symptoms, worsening pain outcomes, psychological distress, overdose, and suicidal ideation and behavior [4]. However, state governments seem reluctant to make similar changes, especially as opioid overdose deaths have increased [20].

The American Academy of Pain Medicine, which had expressed dismay with the 2016 CDC guideline and how it was misapplied by insurance companies, state governments, and healthcare organizations, indicated general support for the 2022 revision [21].

IDENTIFICATION OF DRUG DIVERSION/SEEKING BEHAVIORS

Urine drug tests can give insight into patients who are misusing opioids. A random sample of urine drug test results from 800 pain patients treated at a Veterans Affairs facility found that 25.2% were negative for the prescribed opioid while 19.5% were positive for an illicit drug/unreported opioid [22]. Negative urine drug test results for the prescribed opioid do not necessarily indicate diversion but may indicate the patient halted his/her use due to side effects, lack of efficacy, or pain remission. The concern arises over the increasingly stringent climate surrounding clinical decision-making regarding aberrant urine drug test results and that a negative result for the prescribed opioid or a positive urine drug test may serve as the pretense to terminate a patient rather than guide him/her into addiction treatment or an alternative pain management program [23].

In addition to aberrant urine screens, 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
- 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 [24; 25; 26]:

- 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

interactive activity

View the CDC's video Risk Factors in Opioid Prescribing at https://youtu.be/g9VBbIFurZE. This video addresses the various risk factors likely to increase susceptibility to opioid-associated harms and suggests strategies for mitigating these risks.

FEDERAL AND STATE LAW

In response to the rising incidence in prescription opioid abuse, addiction, diversion, and overdose since the late 1990s, the FDA has mandated opioid-specific REMS to reduce the potential negative patient and societal effects of prescribed opioids. Other elements of opioid risk mitigation include FDA partnering with other governmental agencies, state professional licensing boards, and societies of healthcare professionals to help improve prescriber knowledge of appropriate and safe opioid prescribing and safe home storage and disposal of unused medication [27].

Several regulations and programs at the state level have been enacted in an effort to reduce prescription opioid abuse, diversion, and overdose, including [28]:

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

CONTROLLED SUBSTANCES LAWS/RULES

The U.S. Drug Enforcement Administration (DEA) is responsible for formulating federal standards for the handling of controlled substances. In 2011, the DEA began requiring every state to implement electronic databases that track prescribing habits, referred to as PDMPs. Specific policies regarding controlled substances are administered at the state level [29].

According to the DEA, drugs, substances, and certain chemicals used to make drugs are classified into five distinct categories or schedules depending upon the drug's acceptable medical use and the drug's abuse or dependency potential [30]. The abuse rate is a determinate factor in the scheduling of the drug; for example, Schedule I drugs are considered the most dangerous class of drugs with a high potential for abuse and potentially severe psychologic and/or physical dependence.

STATE-SPECIFIC LAWS AND RULES

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

interactive activity

Visit the NetCE website to view excerpts from specific state rules and regulations relating to the regulation of controlled substances, electronic PDMPs, enacted state legislation, and prescribing guidelines.

https://www.netce.com/learning.php?page=activities&courseid=2435.

PATIENT EDUCATION

Patients and caregivers should be counseled regarding the safe use and disposal of opioids. As part of its mandatory Risk Evaluation and Mitigation Strategy (REMS) for extended-release/long-acting opioids, the U.S. Food and Drug Administration (FDA) has developed a patient counseling document with information on the patient's specific medications, instructions for emergency situations and incomplete pain control, and warnings not to share medications or take them unprescribed [11]. A copy of this form may be accessed online at https://www.fda.gov/media/114694/download.

When prescribing opioids, clinicians should provide patients with the following information [11]:

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

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

There are no universal recommendations for the proper disposal of unused opioids, and patients are rarely advised of what to do with unused or expired medications [31]. According to the FDA, most medications that are no longer necessary or have expired should be removed from their containers, mixed with undesirable substances (e.g., cat litter, used coffee grounds), and put into an impermeable, nondescript container (e.g., disposable container with a lid or a sealed bag) before throwing in the trash [32]. 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 [32; 33]. The FDA provides a free toolkit of materials (e.g., social media images, fact sheets, posters) to raise awareness of the serious dangers of keeping unused opioid pain medicines in the home and with information about safe disposal of these medicines. The Remove the Risk Outreach toolkit is updated regularly and can be found at https://www.fda.gov/drugs/ensuring-safe-use-medicine/safe-opioid-disposal-remove-risk-outreach-toolkit [33]. Patients should be advised to flush prescription drugs down the toilet only if the label or accompanying patient information specifically instructs doing so.

The American College of Preventive Medicine has established best practices to avoid diversion of unused drugs and educate patients regarding drug disposal [31]:

- 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.

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.

DISPARITIES IN PAIN MANAGEMENT

At greatest risk of unrelieved pain from stigma and bias are children, the elderly, racial and ethnic minorities, active duty or military veterans, and those with cancer, HIV, or sickle cell disease. Pain undertreatment in Black patients is especially widespread, from prevalent misperceptions (often unconscious) that this group has higher pain tolerance and is more likely to abuse their opioid prescription [34]. As a result, prescribers, dispensers, and administrators would benefit from considering both the tenets of appropriate opioid prescribing and the impact of culture on experiences of pain and effective pain management.

It is clear that health disparities exist among racial and ethnic minority groups, and this is true for pain management services and medications. A large-scale national study in the United States found racial differences in the prescription of analgesics for patients with migraine, low back pain, and bone fractures [35]. Specifically, Black Americans were less likely to be prescribed analgesics for their pain compared with their White counterparts. Racial minority patients are also more likely to experience longer wait times for medication compared with White patients [36].

Analysis of a national dataset found that Black Americans were less likely to be prescribed opioids for back pain and abdominal pain compared with non-Hispanic White Americans [37]. The authors speculate that racial biases may influence prescribing behaviors. An examination of Medicaid patients who received epidural analgesia during vaginal childbirth also found statistically significant racial/ethnic differences [38]. In this study, 59.6% of the White patients received epidural analgesia, compared with 49.5% of Black Americans, 48.2% of Asians, and 35.2% of Hispanics. Even after the researchers controlled for age, urban/rural residence, and the availability of anesthesiologists, race and ethnicity still predicted epidural analgesia prescribing trends [38].

In a meta-analysis of ethnicity and pain management researchers found that professionals under-rated ethnic minority patients' levels of pain and were less likely to indicate their pain scores on their charts compared with their White counterparts [39]. In addition, Black American and Hispanic patients were less likely to have been given analgesics than White patients.

Studies have not definitively isolated the factors that contribute to these disparities. One of the challenges in understanding health disparities, and particularly pain management disparities, is the fact that racial and ethnic minority groups are heterogeneous [40; 41]. Healthcare professional barriers may include professionals' beliefs about appropriate pain management; lack of training and knowledge about the intersection of pain and culture, race, and ethnicity; lack of culturally sensitive assessment for pain; and expectations about racial and ethnic minority pain patients based on stereotypes [42]. Consequently, practitioners may underestimate and minimize racial minority patients' pain experiences. In a qualitative study, Native American individuals described their complaints of pain being dismissed, receiving inadequate care, and neglected aftercare [43].

Studies have also shown that the language and race/ethnicity of the healthcare professional influences pain management. For example, the ratings of pain tend to be comparable when the patient and healthcare provider speak the same language. When there is a native language, pain ratings tend to diverge. When literacy and language barriers are eliminated, assessment and treatment improve and racial and ethnic minority patients with pain fare better [44]. In addition, healthcare professionals' level of empathy appears to increase when the patient and healthcare professional share the same skin color or are of the same ethnic group [45; 46].

It is important to note that disparities in pain management are not typically intentional. Instead, they are the result of a myriad of issues, including healthcare system, socioeconomic, and cultural factors. However, prescriber and dispenser unconscious bias can contribute to the undertreatment of pain in certain groups. Promoting positive emotions such as empathy and compassion can help reduce implicit biases. This can involve strategies like perspective taking and role playing [47]. In a study examining analgesic prescription disparities, nurses were shown photos of White or Black American patients exhibiting pain and were asked to recommend how much pain medication was needed; a control group was not shown photos. Those who were shown images of patients in pain displayed no differences in recommended dosage along racial lines; however, those who did not see the images averaged higher recommended dosages for White patients compared with Black patients [48]. This suggests that professionals' level of empathy (enhanced by seeing the patient in pain) affected prescription recommendations.

CONCLUSION

Opioid analgesics are approved by the FDA for the treatment of moderate or severe pain. However, individual patients differ greatly in clinical response to different opioid analgesics, and patient populations show widely variable response to the same opioid and dose. These response variations make opioid prescribing challenging. Further, the important role of opioid analgesics is broadly accepted in acute pain, cancer pain, and palliative and end-of-life care, but it is controversial for the management of chronic noncancer pain. Previous opioid prescribing guidelines have been critiqued for lacking a patient-centered approach and failing to emphasize individualization of therapy. This prompted the 2022 revision of the CDC's opioid prescribing guidelines, which is outlined in this course.

Opioids are not a panacea for pain, nor are they safe and effective for every patient. However, they can be a useful tool, and knowledge of medical advances can give clinicians greater confidence to safely and effectively prescribe these drugs.

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Enter the Customer ID and Quick Code found on the back of your booklet, purchase the offer, and complete the test questions from your transcript.

COURSE TEST - #95500 OPIOID SAFETY: BALANCING BENEFITS AND RISKS

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 September 30, 2025.

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

2. All of the following statements regarding opioid use for chronic pain are TRUE, EXCEPT:
- A) *Opioid therapy for chronic pain should be presented as a trial for a pre-defined period.*
- B) *The goals of treatment should be established with all patients prior to the initiation of opioid therapy.*
- C) *Opioids should not be combined with nonpharmacologic and nonopioid pharmacologic therapy.*
- D) *The treatment plan should describe therapy selection, measures of progress, and other diagnostic evaluations, consultations, referrals, and therapies.*

3. Which of the following is one reason that opioids are useful for severe pain at the end of life?
- A) *Unlike nonopioids, opioids do not have a ceiling effect.*
- B) *Opioid side effects do not occur in patients at the end of life.*
- C) *Nonopioid pharmacotherapy is more difficult to administer to patients.*
- D) *Opioids are generally more acceptable to patients and their families than nonopioid options.*

4. What administration route is typically preferred for opioids at the end of life as it is the most convenient and least expensive?
- A) *Oral*
- B) *Parenteral*
- C) *Transdermal*
- D) *Intramuscular*

5. The 2022 revision of the CDC's guidelines for opioid prescribing apply to which of the following patient groups?
- A) *Hospital inpatients*
- B) *Those with sickle cell disease*
- C) *Persons receiving end-of-life care*
- D) *Adults (18 years of age and older)*

6. The CDC states that which of the following is paramount when treating patients with pain?
- A) *Inclusion of opioids in every chronic pain treatment plan*
- B) *Strict adherence to established opioid prescribing guidelines*
- C) *Flexibility to meet the care needs and the clinical circumstances of a specific patient*
- D) *Implementing policies that limit opioid access regardless of pain severity, quality, or effectiveness of nonopioid therapy*

7. Opioids are NOT first-line therapy for which of the following common acute pain conditions?
- A) *Low back pain*
- B) *Headaches, including episodic migraine*
- C) *Pain related to minor surgeries typically associated with minimal tissue injury and only mild postoperative pain*
- D) *All of the above*

8. The CDC recommends which of the following noninvasive, nonpharmacologic approaches for the treatment of subacute or chronic neck pain?
- A) *Exercise therapy*
- B) *Mind-body practices*
- C) *Low-level laser therapy*
- D) *Cognitive-behavioral therapy*

9. Extended-release/long-acting (ER/LA) opioids should be reserved for
- A) *severe, acute pain.*
- B) *moderate, chronic pain.*
- C) *severe, continuous pain.*
- D) *acute pain at the end of life.*

10. In which case might opioid therapy be discontinued abruptly?
- A) *Pregnancy*
- B) *Constipation*
- C) *Signs of impending overdose*
- D) *Desire to discontinue therapy*

11. Following initiation of opioid therapy for subacute or chronic pain or dose escalation, clinicians should evaluate benefits and risks with patients
- A) *within one to four weeks.*
- B) *after one month.*
- C) *every three months.*
- D) *annually.*

12. Clinicians should offer naloxone when prescribing opioids to patients at increased risk for overdose. Which of the following patients would be considered at increased risk for overdose?
- A) *A patient older than 65 years of age*
- B) *A patient with obstructive sleep apnea*
- C) *A patient taking lower dosages of opioids*
- D) *A patient who is also taking an antidepressant*

13. Which of the following statements regarding toxicology testing is NOT in accordance with CDC guidance?
- A) *Clinicians should dismiss patients from care based on a toxicology test result.*
- B) *Clinicians should use unexpected toxicology test results to improve patient safety.*
- C) *When prescribing opioids for subacute or chronic pain, clinicians should consider toxicology testing to assess for prescribed medications as well as other prescribed and non-prescribed controlled substances.*
- D) *Clinicians who believe their patient might be diverting prescription opioids should consider toxicology testing to assist in determining whether prescription opioids can be discontinued without causing withdrawal.*

14. Risks of concurrent opioid and benzodiazepine use are likely to be greater with
- A) *unpredictable use of either medication.*
- B) *use with other substances including alcohol.*
- C) *use of higher-dosage opioids and higher-dosage benzodiazepines in combination.*
- D) *All of the above*

15. For pregnant people with opioid use disorder, which pharmacotherapy is recommended?
- A) *Fentanyl*
- B) *Bupropion*
- C) *Naltrexone*
- D) *Buprenorphine or methadone*

16. 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*

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

18. All of the following should be included in the education of patients prescribed opioids, EXCEPT:
- A) *Product-specific information*
- B) *Risk factors, signs, and symptoms of overdose*
- C) *Instructions for safe sharing of opioids with others*
- D) *Warning and rationale to avoid other central nervous system depressants*

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

20. Implicit biases can impact opioid prescribing practices. Which of the following strategies can promote positive emotions and help reduce implicit biases?
- A) *The use of interpreters*
- B) *Frequent career changes*
- C) *Perspective taking and role playing*
- D) *Increased opioid prescribing for racial/ethnic minority patients*

Smoking and Secondhand Smoke

This course meets the California requirement for smoking cessation therapy education for those who furnish nicotine replacement products.

Audience
This course is designed for healthcare professionals who may intervene to stop patients from smoking.

Course Objective
The purpose of this course is to provide physicians, nurses, behavioral health professionals, and other members of the interdisciplinary team with a formal educational opportunity that will address the impact of tobacco smoking and secondhand exposure in public health and disease as well as interventions to promote smoking cessation among their patients.

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

1. Describe the history of tobacco and its impact on society.
2. Define the prevalence and economic impact of tobacco smoke exposure on public health.
3. Differentiate between available tobacco products.
4. Describe the neurophysiologic effects and addictive components of tobacco smoke.
5. Describe the anatomy and physiology of smoke inhalation, and outline key points in learning of behavior.
6. Define the psychologic and physiologic aspects of smoking dependence.
7. List the common health complications related to smoke exposure.
8. Identify the common comorbid conditions of tobacco users.
9. Describe the developmental complications related to prenatal exposure to smoke.
10. Define the effects of exposure to secondhand smoke for children and adults.
11. Identify the methods of detecting and measuring tobacco smoke exposure.
12. Define thirdhand smoke.
13. Outline the methods of tobacco cessation interventions, including necessary considerations for non-English-proficient patients.
14. Define the treatment modalities for tobacco addiction, including pharmacologic options.
15. Identify strategies to reduce exposure to tobacco smoke.

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

Faculty Disclosure
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INTRODUCTION

Tobacco smoke exposure is a major cause of the nation's most serious and preventable health problems. This course provides comprehensive clinical education on tobacco smoke in primary care and public health. It addresses core competencies as well as knowledge, assessment, and treatment-based competencies of healthcare providers. It covers the history of tobacco, epidemiology of tobacco use, tobacco smoke metabolism, dependence, treatment, and relapse. It also addresses complications associated with direct and indirect exposure to tobacco smoke, effects of prenatal exposure, methods of screening for exposure, and brief intervention training. This course includes a review of available screening tools, predisposing genetic factors, associated risk and protective factors, withdrawal symptoms and treatment, lab testing procedures, diagnostic tools, and age and gender issues.

DEFINITIONS

A clear understanding of tobacco use and smoking is dependent on a knowledge of the basic underlying concepts associated with addiction [1].

Tolerance: The need for greatly increased amounts of the substance to achieve intoxication (or the desired effect) or a markedly diminished effect with continued use of the same amount of the substance.

Withdrawal: Maladaptive behavioral change, with physiologic and cognitive concomitants, that occurs when blood or tissue concentrations of a substance decline in an individual who had maintained prolonged heavy use of the substance. After developing unpleasant withdrawal symptoms, the person is likely to take the substance to relieve or to avoid those symptoms, typically using the substance throughout the day, beginning soon after awakening.

Substance use disorder: A cluster of cognitive, behavioral, and physiologic symptoms indicating that the individual continues using the substance despite significant substance-related problems. There is also an underlying change in brain circuits that may persist beyond detoxification.

HISTORY OF TOBACCO USE AND RESTRICTION

Tobacco was the first export of the New World and was marketed in Europe as a remedy for stress, ulcers, headaches, asthma, and even rheumatism. Tobacco's botanical name, *Nicotiana tabacum*, is derived from Jean Nicot, a French ambassador to Portugal who, convinced of tobacco's medicinal value, sent the plant's seeds to the royal family in France [2].

Tobacco product use has been discouraged in the United States and abroad for centuries. In 1586 the first recorded tobacco prohibition was issued by Pope Sixtus V, who declared it a sin "for any priest to use tobacco before celebrating or administering communion." In 1604, King James I published *A Counterblaste to Tobacco*, describing smoking tobacco as, "a custome lothsome to the eye, hatefull to the Nose, harmefull to the braine, [and] dangerous to the Lungs" [3]. Tobacco use and distribution saw further restrictions across the globe in the early 1600s. King James I levied heavy taxes on tobacco, the czar of Russia exiled tobacco users, and the Chinese executed persons caught selling tobacco [4].

However, in contrast to strict regulations found elsewhere in the world, tobacco was brought to the United States as a cash crop. The 1880s saw the invention of an automated cigarette-making machine, which paved the way for cigarettes to become the predominant form of tobacco with the start of World War I. The twentieth century also experienced the first major outcry against tobacco in the United States. Though medical concerns were suggested, the first tobacco prohibition movements in the United States were primarily driven by religious and moral motivations. Groups including religious leaders, the Women's Christian Temperance Union, and the Non-smokers Protective supported efforts for prohibition of tobacco. However, strong public resistance against alcohol prohibition also led to the repeal of tobacco restrictions, and by the 1930s these restrictions had all but vanished [5].

One of the lesser known consequences of World War II was that German smoking research and corresponding social change were not acknowledged by the rest of the world. In the 1930s and early 1940s, Germany conducted an aggressive anti-smoking campaign based on medical research from the 1920s and 1930s, which elucidated the carcinogenic effects of smoking. As part of the German movement aimed to preserve a racial "utopia" of pure, healthy Germans, they banned smoking in the workplace, imposed cigarette taxes, restricted advertising and farming, and implemented programs to eliminate smoking [6; 7].

Associations between smoking and cancer were not published in the United States until the 1950s and 1960s. The 1964 publication *Smoking and Health: Report of the Advisory Committee to the Surgeon General* led to immediate political notice of the tobacco issue and the advent of programs and policies to reduce smoking [8]. Anti-tobacco policies have included taxation on tobacco products, increased insurance premiums, warning labels, public health campaigns, and restrictions on tobacco sales to minors, smoking in public areas, and tobacco marketing. Prior to 1964 there were few if any laws regulating involuntary secondhand smoke (SHS) exposure. Studies revealing the detrimental effects of SHS to nonsmokers led to new anti-smoking legislation. As of June 2009, the General Services Administration (GSA) has established smoke-free environments for federal facilities. Interior areas previously designated for smoking have been closed and smoking is prohibited in courtyards and within 25 feet of doorways and air intake ducts in outdoor spaces [9]. Further, nearly all 50 states have laws restricting smoking in places such as schools, public transportation, government buildings, elevators, and restaurants. In accordance with federal law, smoking is prohibited on buses, trains, and domestic airline flights. Such laws have decreased cigarette consumption by making smoking less socially acceptable and more inconvenient [5].

On June 22, 2009, President Barack Obama signed HR1256: The Family Smoking Prevention and Tobacco Control Act. This was enacted as a result of several findings made by Congress, specifically that almost all new users of tobacco products are younger than the minimum legal age to purchase such products. Under this law, the U.S. Food and Drug Administration (FDA) now has the authority to regulate tobacco products [10]. The FDA had previously attempted to assert jurisdiction under the Food, Drug, and Cosmetic Act in 1996 to regulate tobacco advertising, labeling, and purchasing restrictions (e.g., federal minimum age of 18 years and requiring retailers to check identification). However, the tobacco industry retaliated by suing the federal government, as there was no set legislation to give the FDA this authority. As a result, all FDA regulations were dropped [11]. Due to the 2009 law, the FDA can now establish a minimum age of sale of tobacco products, test and report on tobacco product ingredients/additives, prohibit cigarettes from containing any flavors other than tobacco or menthol, and apply the same restrictions on labeling and advertising of cigarettes to smokeless tobacco products. Of note, this law states that the FDA cannot ban existing products or require nicotine be eliminated from any product.

In 2017, the FDA unveiled a comprehensive plan on tobacco and nicotine regulation to reduce the number of preventable deaths caused by smoking and tobacco use [472; 474]. The two key areas of focus of this plan are reducing the nicotine levels in combustible cigarettes to render them minimally or nonaddictive and harnessing new forms of nicotine delivery that could allow currently addicted adult smokers to get access to nicotine without many of the risks associated with using combustible tobacco products. Similar to the 2009 policy, this plan also explores the extent of tobacco flavoring in attracting youth and new smokers; menthol flavoring will be included in this plan. Of note, this policy only affects newly regulated tobacco products and will not affect any current requirements for cigarettes and smokeless tobacco. In 2019, President Donald Trump signed legislation to amend the Food, Drug, and Cosmetic Act to raise the federal minimum age to purchase all tobacco products (including e-cigarettes) from 18 to 21 [475]. It is now illegal to sell tobacco products to anyone younger than 21 years of age.

As of April 2022, there are three companies approved to sell 15 modified-risk tobacco products (MRTPs), including cigarettes, smokeless tobacco (snuff), and a heated tobacco product [476]. To receive a MRTP authorization, the FDA must find that the product is less likely to cause disease, including cancer, cardio-

vascular disease, emphysema, and bronchitis, than traditional cigarettes and must discern whether those who do not use tobacco products would start using the product and whether existing tobacco users who would have otherwise quit would switch to the modified risk product instead [477].

PREVALENCE AND ECONOMIC IMPACT OF SMOKING

Approximately 480,000 Americans die each year as a result of active and/or passive smoking-related health consequences [12]. Despite the seemingly well-known and highly publicized health consequences of smoking, 13.9% of the U.S. population 18 years of age or older are current cigarette smokers [460]. Former U.S. Assistant Secretary for Health Howard Koh asserted that although evidence-based tools were successful in substantially reducing smoking prevalence between 1997 and 2004, efforts were not applied to their full potential nationwide, limiting the efficacy of anti-smoking campaigns [14]. Other experts have attributed declines in cigarette smoking to anti-smoking advertisements, stigma, smoking bans, and increased taxation [460]. Evidence-based tools remain valuable, indicated by slow, steady downward prevalence trends since 1997. However, they are only useful if they reach an audience. These tools seem not to be preventing the initiation of new smokers, despite the overall reductions in use [14; 15].

Nearly 1.6 million Americans initiated cigarette smoking in 2019, continuing a downward trend noted since 2006 (down from approximately 2.5 million); 34% of these were 12 to 17 years of age [13]. About one-third of new smokers will ultimately die from a smoking-related illness [16]. Higher levels of education are correlated with a lower likelihood of having smoked cigarettes in the past month [13]. The number of first-time cigar users is slowly declining, from 3.4 million in 2006 to 2.1 million in 2019 [13]. In 2019, use in the past year of any tobacco product was highest among American Indians/Alaska Natives (39.8%) followed by persons of two or more races (35.2%), White Americans (28.6%), Black Americans (27.2%), Hispanics (19.5%), and Asians (13.2%) [13].

Approximately 41,000 adult nonsmokers die each year from exposure to SHS, and this continues to be a significant environmental risk in the United States [12]. In a 2009 study, the prevalence of smoking in New York City was lower than the national average (23.3% vs. 29.7%), but the proportion of nonsmoking adults with elevated cotinine levels was higher (56.7% vs. 44.9%), especially among Asians, even nearly two years after implementation of smoke-free workplace legislation [20]. This finding was attributed to the large amounts of people living in close proximity (26,000 people and 10,000 housing units per square mile vs. the national average of 80 people and 33 housing units per square mile) [20]. In a 2017 study, Perlman and colleagues examined cotinine levels in New York City nonsmokers, and found that 37.1% had elevated levels [17]. It is thought that this reduction (from 56.7% in the earlier study) is a result of smoke-free air policies enforced within the previous 10 to 15 years. The researchers also noted that greater population density and pedestrian exposure continued to contribute to a high number of nonsmokers with elevated cotinine levels compared with the national average [17]. Nonsmoking individuals with the highest cotinine serum concentrations tended to be living in high-poverty neighborhoods, have lower educational attainment, be 20 to 39 years of age, report non-Hispanic Black race, and be male.

Tobacco use is one of the most expensive addictive behaviors in the United States. In 2015, an estimated 299.9 billion cigarette stick equivalents of combustible tobacco products (based on the weight of 0.0325 ounces of tobacco per cigarette) were consumed in the United States, of which 267 billion were cigarettes [21]. The Federal Trade Commission (FTC) reported that 203.7 billion cigarettes were sold in the United States in 2020 [54]. Americans spent $84.8 billion on cigarettes alone (10.6 billion packs) in the 2021 fiscal year [23].

Smoking-related costs in the United States are staggering. The total annual public and private healthcare expenditures caused by smoking are estimated to be greater than $300 billion, including nearly $170 billion in direct medical costs and more than $156 billion in lost productivity related to premature death and exposure to SHS [12].

TOBACCO AND NICOTINE PRODUCTS

Cigarette smoking is on the decline in the United States, but use of other tobacco products is not [13; 21]. In addition to a rise in use of smokeless tobacco, people across the United States (especially youth) are using e-cigarettes, cigars, cigarillos (small cigars), hookahs, kreteks, pipes, and bidis (or beedis) [18; 25]. Unfortunately, each of these products is just as dangerous (if not more so) as use of cigarettes. Cigarettes are defined by the U.S. Department of the Treasury as "any roll of tobacco wrapped in paper or in any substance not containing tobacco," while cigars are defined as "any roll of tobacco wrapped in leaf tobacco or in any substance containing tobacco" [26]. Cigars also differ from cigarettes in processing; they consist of filler, a binder, and a wrapper, all made of air-cured and fermented tobaccos [27]. Cigars show significant variability in physical and chemical characteristics, with total nicotine content ranging from 10.1 mg to 444 mg per cigar, length ranging from 68.0 mm to 213.5 mm, and diameter ranging from 8.0 mm to 20.5 mm [28]. Due to their size and makeup, smokers can spend up to an hour smoking a single cigar; therefore, its ensuing effects (e.g., rates of cancer, chronic obstructive pulmonary disease [COPD]) are more pronounced. Cigarillos, or "little cigars," are generally about half the size of a normal cigar, weighing 1.5–3 g on average [29]. Many types are made to look like cigarettes and are sold in packs of 20 with filter tips. Cigarillos are perceived as a less addictive, less harmful, and less expensive alternative to cigarette use [30; 31].

Nicotine—the identified drug in tobacco—is highly addictive, and flavors enhance nicotine's addictive effects. Flavors significantly increase tobacco use because they enhance its appeal, especially among adolescents and young adults [481]. More than 90% of current smokers started smoking as teenagers, and it is estimated that 80% of youths who used tobacco began with flavored tobacco products [481]. Additionally, flavors, such as menthol, mask the harshness and bitterness of tobacco, sustain tobacco dependence, and hinder cessation.

Aggressive and targeted marketing of flavored tobacco products has long been an industry tactic intended to lure young people into experimentation with tobacco products, resulting in addiction and, consequently, premature death. The tobacco industry has especially targeted Black and LGBTQ communities with predatory marketing of menthol cigarettes and flavored cigars. As of 2019, the FDA found there were 18.5 million people in the United States who smoked menthol cigarettes, which are disproportionately used by marginalized populations [481]. Nearly 85% of African American smokers use menthol cigarettes.

An estimated 9,000 Americans die prematurely from cigar smoking each year. Additionally, an annual health care expenditure of $1.8 billion is attributed to cigar use. Flavors are critical to cigar usage. There is a greater frequency of smoking by adults who smoke flavored cigars compared with those who smoke unflavored cigars. In 2020, an estimated 960,000 youths smoked a cigar at least once in 30 days, with almost 60% reporting that they used flavored cigars.

Due to increased federal taxation on cigarettes, cigarette tobacco, and small cigars, many consumers apparently switched to smoking products virtually identical to cigarettes or small cigars, but classified as large cigars, or from smoking cigarette rolling tobacco to smoking "pipe tobacco" [22]. Subsequent to the 2009 tax increase and intensified FDA regulation, many companies simply relabeled cigarette rolling tobaccos as pipe tobaccos (not subject to increased taxation) [21]. Sales of "pipe tobacco" increased from 5.2 million pounds in 2009 to 43.7 million pounds in 2013 (a 740% change) while rolling tobacco sales dropped from 21.3 million pounds to 3.8 million pounds [22]. Following a similar relabeling and marketing effort for small cigars, sales of large cigars jumped from 5.8 billion sticks in 2009 to more than 12.4 billion sticks in 2013, while small cigars decreased from 5.7 billion sticks to 0.7 billion sticks in the same years. In 2016, the FDA extended its limitations for tobacco products to include e-cigarettes, vaporizers, and other electronic nicotine delivery systems [458]. As a result, these products must include warnings and manufacturers must submit documentation to the FDA for review and limit sales to persons 21 years of age or older. The goals of these regulations are to increase public health awareness and, especially, reduce marketing and sales to adolescents and young adults, who are commonly targeted by providing tobacco flavors including apple, cherry, cream, grape, "jazz," strawberry, and wine. Before this ruling, there were no federal laws restricting sales of these types of products, but an alarming increase in unregulated tobacco products, especially among high school students, prompted the FDA to enforce regulations. In 2018, the FDA issued more than 1,300 warnings and fines to retailers who illegally sold e-cigarette products to minors [464].

Prohibiting menthol in cigarettes has been proposed as an approach to decrease the appeal of cigarettes and ease of smoking, thus minimizing the likelihood of smoking initiation and subsequent nicotine dependence. It would also improve the health of current smokers by decreasing cigarette consumption and increase the likelihood of cessation. This would also minimize death and disease associated with exposure to secondhand smoke. The FDA estimates that prohibiting menthol in cigarettes would prevent 654,000 premature deaths in 40 years [481]. The FDA also found prohibiting menthol would advance health equity, because menthol use is more prevalent in marginalized communities, especially among Black smokers, and prohibiting menthol would lessen the health harms those communities disproportionately bear. It is estimated that the menthol prohibition would prevent 238,000 premature Black deaths in 40 years [481]. In April 2022, the FDA proposed a rule banning menthol flavoring added to cigarettes [481].

The FDA also proposed a rule that would prohibit flavors (including menthol) in cigars and their components and parts. As noted, flavors appeal to young people, and cigar flavors come in many varieties (including spice, strawberry, grape, banana, licorice, menthol, and chocolate) that make cigars easier to smoke.

Similar to the proposed ban on menthol in cigarettes, this proposed rule would prohibit the manufacture, distribution, or sale of flavored cigars in the United States. Here, too, the FDA focuses on the supply side of the market and would not prohibit individual consumers from possessing or using flavored cigars.

The proposed rule comprehensively defines cigars—which are made in different sizes and shapes—as "a roll of tobacco wrapped in leaf tobacco or any other substance containing tobacco" [481]. This broad definition captures many tobacco products (including little cigars, cigarillos, and large cigars) and should guard against manufacturers skirting the ban by switching to other products that closely resemble other prohibited flavored tobacco products. The flavor prohibition would also apply to cigar "components or parts," so products such as filters, blunt wraps, or tips also could not be flavored [481].

The rise of e-cigarettes in the past decade has introduced new variables in the prevention and treatment of nicotine addiction. Originally marketed as a smoking cessation tool, e-cigarettes are electronic products that typically deliver nicotine in the form of an aerosol [456]. Most e-cigarettes consist of a cartridge (which holds a liquid solution containing varying amounts of nicotine, flavorings, and other chemicals), a heating device (vaporizer), and a power source (usually a battery) [457].

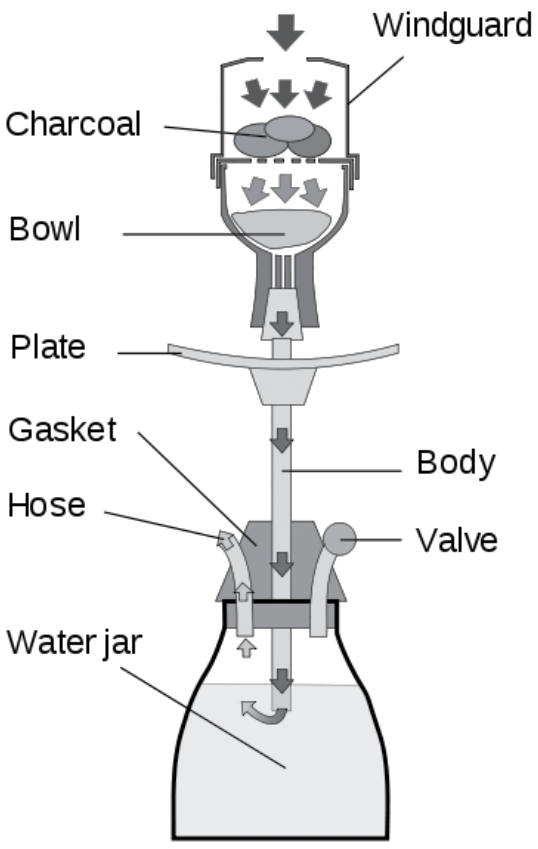
In many e-cigarettes, puffing activates the battery-powered heating device, which vaporizes the liquid in the cartridge. The resulting aerosol or vapor is then inhaled (called "vaping") [457]. It is unclear if this delivery method decreases the risks seen with conventional tobacco smoking; however, it does introduce the risks of toxicity associated with consumption of the potent e-liquid, including heavy metals (e.g., cadmium, chromium, lead, manganese, nickel) that are also emitted from the heating element and heated plastic [478].

In 2020, 3.7% of adults were current every day or some days e-cigarette users. Adults 18 to 24 years of age (9.4%) have the highest rate of e-cigarette use, followed by those 25 to 44 years of age (5.2%), 45 to 64 years of age (2.2%), and older than 65 (0.6%) [456]. Use is much higher among men (4.6%) than women (2.8%). Current use of e-cigarettes among high school students skyrocketed from 1.5% in 2011 to 11.3% in 2021, making it the number one form of nicotine used among high school-age youth [331; 459]. E-cigarette use is particularly prevalent in White students (14.5%) and is less prevalent among Black (5.9%) and Hispanic (7.6%) students. Slightly more high school age girls (11.9%) than boys (10.7%) use e-cigarettes. In 2021, 2.8% of middle school students were current users of e-cigarettes [331].

According to the Centers for Disease Control and Prevention (CDC), large cigar consumption increased 115% from 2000 to 2020, with cigar smoking being the third most common form of tobacco use among youth [32; 33; 331]. Cigar use is twice as common among Black versus White high school students and is much more common among boys than girls. However, it has been shown that adolescent (and likely adult) cigar use is significantly underestimated due to systematic misreporting on statewide surveys, which is mainly attributed to the language and definitions used in questions that assume knowledge of all types of cigars [34]. For example, it was found that more than half of Black & Mild (brand of cigars and cigarillos) users did not report any cigar/cigarillo use on a 2009 Virginia survey, largely because the usage of the terms "cigar" or "cigarillo" for this (and other similar products) is not common in the youth- or culture-specific lexicon.

Bidis consist of sun-dried tobacco, finely ground and rolled into a leaf of the *Diospyros melanoxylon* plant native to India. They contain concentrated tobacco, with an average 21.2 mg/g of nicotine compared with 16.3 mg/g of nicotine in filtered and 13.5 mg/g in unfiltered cigarettes, but have less total nicotine because they are shorter [35]. Nonetheless, an unfiltered bidi can release three to five times more tar and nicotine and contain more ammonia and carbon monoxide (CO) than a regular cigarette. Bidis look similar to small cigars or marijuana cigarettes and are available filtered or unfiltered in many flavors, including vanilla, chocolate, strawberry, cherry, and menthol [36]. Bidis are not commonly used in the United States, and sale and distribution is banned in some states (e.g., Illinois, Vermont, West Virginia). However, these products are available on the Internet [37].

SCHEMATIC OF A WATERPIPE



Source: [46] *Figure 1*

Kreteks, or clove cigarettes, are composed of a mixture of tobacco (60% to 80%) and ground clove buds (20% to 40%), available with or without filters [38]. A popular, representative kretek brand contains less nicotine than popular cigarettes (7.39 mg), but smokers extract equal amounts of nicotine by altering smoking behavior [39]. For example, clove cigarettes can be smoked slower, using more puffs. Overall, smokers will do whatever is necessary to achieve plasma levels of nicotine comparable to their usual brand of cigarette.

A hookah is a type of waterpipe comprised of a head or bowl, plate, body, jar, hose, and mouthpiece (***Figure 1***). The body of the hookah fits down into the jar, which is partially filled with water, although any liquid (e.g., alcohol, juice) can be used. Tobacco is placed in the bowl at the head of the body and covered with a filter, such as perforated tin foil, and then burning embers or charcoal is placed above it (and sometimes covered by a cap). The hot air from the charcoal roasts the tobacco and the ensuing smoke is passed down into the liquid in the jar where it is partially filtered, diluted, and cooled. The smoke then bubbles up and passes through the hose and mouthpiece for inhalation. Repeated inhalation is required to keep the

tobacco burning. The plate stores dead coals/embers. The types of tobacco used for hookah are *ajami* or *tumbak*, which is a pure, dark tobacco paste; "honeyed" or *tobamel* or *maassel*, containing 70% honey or molasses and featuring flavors (e.g., apple, mango, banana); or *jurak*, which may be sweetened or contain fruits or oils. It is commonplace to use 10–20 g at a time, and these tobaccos may be mixed with other drugs [40]. Smoking sessions last up to an hour or longer, and it has been reported that the nicotine content of the tobacco used for hookah is higher than that in cigarettes [41]. Thus, the smoker is exposed to a higher volume of smoke for longer periods (not to mention those in the vicinity). A report from the World Health Organization states that a hookah user may inhale as much smoke in one session as a cigarette smoker would after consuming at least 100 cigarettes [42]. Contrary to popular belief, waterpipe smoking is not safer or less addictive than cigarette smoking [43]. The FDA began regulating the manufacture, import, packaging, labeling, advertising, promotion, sale, and distribution of tobacco mixtures used for hookah in 2016 [24]. Hookah smoke contains higher concentrations of CO, nicotine, tar, heavy metals, and carcinogens, likely because of its method of use (i.e., tobacco mixtures heated by quick-burning charcoal or wood embers and inhalation through use of a plastic hose for an hour or longer) [44; 45]. It is also common to share a hookah, so users are also at risk of exposure to infections (e.g., herpes due to sharing of the mouthpiece) [46]. Hookah pipe smoking may be a gateway to cigarette smoking and other drug use. Although policies are in place to ban smoking in many public places, many times, hookah use is exempt because it is done in places which identify themselves as "tobacco bars," waterpipe smoking areas are set up outside, or the smoking is done in places where tobacco is sold.

TOBACCO-RELATED CONCEPTS

For many years, efforts to make cigarettes "safer" have been pursued as a compromise solution [48]. Filtering devices have been used to selectively reduce cigarette smoke constituents for almost 60 years [49]. Studies from the 1970s concluded that charcoal filters can remove up to 66% of ciliotoxic agents from mainstream smoke, and cellulose acetate filter tips can eliminate up to 75% of *N*-nitrosamines, which are known volatile carcinogenic compounds [50; 51]. However more recent studies have shown that neither type of filter is effective for reducing the free radical and reactive oxygen species content in the particulate or gas phase of cigarette smoke [52]. Additionally, remnant (i.e., post-filter) aqueous tar can cause the formation of DNA adducts, particularly the mutagenic 8-Oxo-2'-deoxyguanosine (8-oxo-dG).

The FTC performed tar, nicotine, and CO content measurements in all domestic cigarette varieties sold in the United States, which numbered almost 1,300 in 1998, the last year the report was conducted. The FTC defines tar as the particulates of cigarette smoke minus water and alkaloids, such as nicotine, detected using a method developed in 1966 [53]. In 2020, 99.8% of cigarettes sold in the United States had filters, and the FTC reported that in 2016, 87.9% of the market share of cigarettes had less than 15 mg of tar (manufacturer reported), compared with only 2% in 1967 [53; 54]. Nevertheless, epidemiologic evidence does not indicate that modern cigarettes are any safer. Smokers participating in the Cancer Prevention Study II (CPS-II) from 1982 to 1988 manifested an almost sixfold increase in lung cancer death compared to Cancer Prevention Study I (CPS-I) participants during 1959 to 1965, even though filter tips were introduced in the 1950s and only the latter group benefited from their implementation [55]. Smoking pattern compensation and use of stronger tobacco strains may be at least partially responsible for this paradoxical trend.

Filter vents, usually shaped in rings of small perforations along the filter, allow air to mix with smoke, diluting the amount of tar, nicotine, and CO detected by the FTC method [53]. Interestingly, as many as 58% of smokers of cigarettes with tar less than approximately 7% (formerly labeled "ultralight") and 53% of smokers of cigarettes with tar levels of 8–14 mg of tar (formerly labeled "light") inadvertently cover these vents to some extent [56; 57]. Blocking half of the vents of a 4.4 mg tar cigarette, as is done when smokers pinch the cigarette with their fingers or hold the cigarette in their lips, increases yields of tar by 60%, nicotine by 62%, and CO by 73% [58]. Poor reliability of the FTC method is further made evident in the work of Byrd and Robinson, who concluded that the "FTC yield cannot precisely predict nicotine uptake for an individual smoker" and "nicotine uptake by smokers is influenced by...many possible smoker-controlled parameters" [59]. Interestingly, this publication originates from the R.J. Reynolds Tobacco Company. Another contributing factor to the increase in mortality related to smoking may be the concentration of nitrate in tobacco leaves, one of the most important precursors for the endogenous formation of *N*-nitrosamines during smoke inhalation [60]. Cigarette nitrate content has increased from 0.5% in the 1950s to 1.2% to 1.5% in the late 1980s, possibly due to the increased use of chemical fertilizers and the introduction of plant ribs and stems into U.S. tobacco blends [61]. The carcinogenic potential of nitrosamines has been well documented.

All in all, efforts to reduce the health hazards of smoking leave much to desire, and in spite of filter tip implementation and reportedly lower tar values, cigarettes remain a serious health hazard, affecting smokers and those around them.

CIGARETTE SMOKE

Cigarette smoke is a complex mixture of more than 7,000 components, including nicotine, aromatic hydrocarbons, sterols and oxygenated isoprenoid compounds, aldehydes, nitriles, cyclic ethers, and sulfur compounds [62; 63; 134]. At least 70 of these components are known to cause cancer [134]. Firsthand smoke is defined as the smoke that the smoker inhales. Smoking tobacco products also generates environmental tobacco

smoke, also known as SHS and passive smoke, which consists of both exhaled mainstream and sidestream smoke. These two forms of smoke differ in chemical composition and have different temperatures and oxygen levels during generation. The burning end of a cigarette produces sidestream smoke, which in turn is the main component of SHS. Some known toxins of the thousands of chemical constituents in tobacco smoke are also present in SHS, including benzene, cadmium, ethylbenzene, formaldehyde, hydrazine, lead, limonene, methylamine, methylene chloride, nicotine, pyridine, toluene, and radioactive polonium-210 [64; 65; 66]. One study identified indoor air pollution from SHS as 10 times greater than diesel car exhaust [67].

Many of the diseases once thought only to be caused by active smoking have now been authoritatively linked to environmental tobacco smoke [62; 68]. This finding is not surprising considering that many of the harmful components found in both firsthand smoke and SHS are more concentrated in SHS. Nicotine, tar, nitric oxide, and CO levels have been shown to be nearly twice as concentrated in SHS. Other harmful chemicals preferentially formed in SHS include carcinogenic aromatic amines (e.g., o-toluidine, 2-naphthylamine, and 4-aminobiphenyl) [62; 65; 69]. Three times greater concentrations of polonium-210 exist in sidestream smoke, because most of the radionuclides are not deposited in the smoker's lungs, as with mainstream smoke [479].

POTENTIALLY THERAPEUTIC COMPONENTS OF TOBACCO

According to Lans et al., the crushed leaves of *Nicotiana tabacum* are applied to wounds in Guatemala, and tobacco steam vapor is considered a cure-all in Latin America and the Caribbean. In addition to its most addictive component, nicotine, the tobacco plant contains many enzymes, flavonoids, and coumarins and malic, citric, and phenolic acids [70]. In a case-control study by Sandler et al., tobacco use and secondhand exposure (e.g., parents had smoked) reduced the risk of developing ulcerative colitis; however, at least one meta-analysis found that nicotine therapy for existing ulcerative colitis, while better than placebo, was not more effective than standard treatment and was associated with significant adverse events [71; 430]. Plants of the genus *Nicotiana* have been manipulated in various experiments to express proteins that may be used medicinally. Indeed, transgenic tobacco plants have been used in the development of vaccines for measles, lymphoma, and diabetes [72; 73; 74].

ANATOMY AND PHYSIOLOGY OF SMOKE INHALATION

Administration of any drug via smoking is a highly efficient route, allowing rapid delivery to the brain. This act involves inhalation of a small volume of smoke (an average of about 35 mL for cigarettes) into the mouth from which it is drawn into the lungs [75]. The breathing pattern employed is different from normal tidal breathing in that a smoker's inhalation is deeper and more rapid, drawing the smoke in as a bolus at the beginning of inhalation [76]. However, this pattern varies greatly between smokers and during the course of consuming a single cigarette [77]. Uptake of smoke ingredients is determined by many factors, including chemical composition, smoker's inhalation behavior, lung morphology, and physiologic parameters such as tidal volume, vital capacity, rate of breathing, and rate of lung clearance [78]. Individual differences in size, metabolism, and genetics may also play a role. One hypothesis suggests that stimulation of nicotine-sensitive receptors in the upper airway by various elements of smoke governs the amount inhaled. Indeed, application of a topical anesthetic to the upper airway reduces the quantity of smoke inhaled [79].

Tobacco smoke consists of gaseous and particulate phases, with the particulate phase comprising about 8% of the total volume [76]. Particulate deposition depends on the size, shape, and hygroscopicity (ability to absorb water vapor) of the particles as well as the duration and depth of inhalation [77]. Smoke particles range from 0.1–1.0 mm in diameter as they exit a cigarette, doubling in size within half a second due to aggregation, cooling, and condensation [80]. Larger particles (1–5 mm) are likely to deposit in the trachea and bronchi, whereas smaller particles (0.01–1 mm) reach bronchioles, alveolar ducts, and alveoli. Irregularly shaped or fibrous particles tend to get trapped at branching points, although some of these particles can travel on to the alveoli [81]. Interestingly, smoking seems to result in a greater apical and central distribution of particles than normal tidal breathing. This finding may help to explain the pathogenesis of centrilobular emphysema [76].

Cigarettes deliver nicotine in a pulsatile manner, with plasma concentrations reaching their peak within 1.5 to 3 minutes of the commencement of smoking and gradually returning toward baseline within two to three hours [82]. Thus, nicotine levels rise and fall throughout the day with each cigarette smoked, declining to minimum amounts found in nonsmokers in the morning after the extended abstinence period of sleep. Such continuous flux in blood nicotine levels locks the user into an endless cycle of ups and downs and is thought to lead to the commonly held notion that smoking has a positive effect on mood. Considering smokers begin to experience withdrawal symptoms within hours of their last cigarette, and because these unpleasant effects are almost completely alleviated by smoking, this perception is hardly surprising. Daily repetition of this process links these perceived positive health benefits to the act of smoking in the smoker's mind and often results in the false identification of cigarettes as an effective form of self-medication [83].

LEARNING OF BEHAVIOR

What is it about smoking that makes it so addictive? On one hand, this form of drug delivery is very efficient; inhaled nicotine is absorbed through pulmonary rather than systemic circulation and can reach the brain within 10 to 20 seconds

[84]. Once inside the central nervous system (CNS), nicotine stimulates release of dopamine from the nucleus accumbens, much like the use of cocaine and amphetamines, leading to the feeling of satisfaction and well-being. Given such rapid central reinforcement, it is not surprising that tobacco can become highly addictive. On the other hand, familial and social influences often play a crucial role in determining who might start smoking, quit, or become dependent [83]. For example, one study managed to train a small percentage of rhesus monkeys to smoke, but with such difficulty that it concluded that "environmental factors play the primary role in developing smoking behavior" [85].

Experimenting with smoking usually occurs in the early teen years and is predominantly driven by psychosocial motives [83]. For a first-time user, lighting a cigarette is a symbolic expression of autonomy and independence; acquisition of the desired image is often a sufficient incentive for a novice smoker to tolerate the body's rejection of the first few cigarettes. Despite an admitted awareness of at least some of the deleterious effects of smoking, in 2018, 1 in 4 high school students and 1 in 14 middle school students admitted to using a tobacco product in the past 30 days [135]. Almost all people (90%) who will smoke as adults have started doing so by 18 years of age, and the earlier a person begins, the more likely they are to continue [135]. Within a year, adolescents inhale the same amount of nicotine per cigarette as adults, and they too experience the craving and withdrawal symptoms associated with nicotine addiction [83]. By 20 years of age, 80% of smokers regret ever having started.

The U.S. Preventive Services Task Force recommends that primary care clinicians provide interventions, including education or brief counseling, to prevent initiation of tobacco use among school-aged children and adolescents.

(https://jamanetwork.com/journals/jama/fullarticle/2765009. Last accessed June 15, 2024.)

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.)

Much research has been dedicated to uncovering reasons for the development of a smoking habit. Risk factors include [86]:

- Presence of a smoker in the household
- Single parent home and/or strained relationship with parent
- Comorbid psychiatric disorders
- Low level of expressed self-esteem and self-worth
- Poor academic performance
- In boys, high levels of aggression and rebelliousness
- In girls, preoccupation with weight and body image
- Increased adolescent perception of parental approval of smoking
- Affiliation with smoking peers
- Availability of cigarettes

In addition, twin studies revealed a significant genetic contribution to both smoking initiation and dependence [87; 88].

RITUALISM

In practice, many find the very act of smoking a cigarette ritualistic and calming. The process of "packing" cigarettes by tapping the box on the palm of a hand, removing a cigarette, lighting it, inhaling, and watching the smoke as it is exhaled all contribute to the perceived need to smoke. Some go so far as to claim that they "would not know what to do with their hands" if they were to stop smoking [83]. An investigation using denicotinized cigarettes illustrated that the sensorimotor experience of smoking makes a significant contribution to the perceived satisfaction [89].

MEDIA INFLUENCE

Mass media is another factor that contributes to the learning of smoking behavior. Historically, the tobacco industry recruited new smokers by associating its products with fun, excitement, sex, wealth, power, and a means of expressing rebellion and independence [90]. Such promotional efforts have proven to be especially effective on teenagers, a particularly lucrative market with a lifetime of cigarette consumption ahead of them [91]. Although at present tobacco companies can no longer directly advertise to teenagers, they retain the most potent form of marketing: movies. Smoking in film is a "more powerful force than overt advertising," perhaps because the audience is generally unaware of any sponsor involvement [92]. Philip Morris, one of the world's leading tobacco companies, stated in their 1989 marketing plan, "We believe that most of the strong, positive images for cigarettes and smoking are created by cinema and television" [90]. Although television is taking a more socially responsible stance on the subject of on-air tobacco use, movies continue to model smoking as a socially acceptable behavior, portraying it as a social behavior or a way to relieve tension [93; 94]. A study exploring the connection between a child's professed favorite movie star and that actor's on-screen smoking history revealed "a clear relation between on-screen use and the initiation of smoking in the adolescents who admire them" [95]. Tobacco use in movies, albeit falling through the 1970s and 1980s, increased significantly after 1990 [90]. Furthermore, despite declining tobacco use and increasing public understanding of the dangers of nicotine, smoking in movies returned to the levels observed in the 1950s, when it was nearly twice as prevalent in society as in 2002 [96]. A study analyzing the content of the top 25 grossing films each year from 1988 to 1997 found that 87% of movies depicted tobacco use, with an average of 5 occurrences per film. The vast majority of tobacco use was portrayed as experienced use (91.5%) and rarely did it represent a character's first use (0.3%) or a relapse from a previous quit attempt (0.5%). Despite the fact that R-rated movies contained most tobacco exposure and

were more likely to feature a major character using tobacco, about 60% of the total coverage of smoking occurred in youth-rated films (G, PG, and PG-13). Negative reactions to tobacco use, including comments about health effects or gestures such as coughing, were depicted in only 5.9% of the occurrences. Unrealistic portrayal of cigarette smoking on the big screen may help to explain the somewhat surprising finding that children of nonsmoking parents are especially susceptible to the effects of movie smoking exposure [93]. Between 2002 and 2017, 6 out of every 10 movies rated PG-13 contained smoking or tobacco use, with historically high average of occurrences per film in 2016 (34 per film) and 2017 (29 per film), prompting many health groups to advocate for the requirement of an R rating (i.e., younger than 17 years of age require accompanying adult) for any films containing tobacco use. Researchers estimate that requiring a R rating would reduce the number of teen smokers by 18%, preventing up to 1 million deaths from smoking in the future [184]. Since May 2007, the Motion Picture Association of America (MPAA) has made smoking a factor in assigning ratings to films. The pervasiveness of tobacco use, context in which smoking appears, and whether or not the act is glamorized are all taken into account by film raters [97].

GENETICS

It has been suggested that high genetic vulnerability to cigarette smoking may explain why some people begin and continue to smoke despite associated risks [98]. Twin studies found significant heritability for persistence of smoking versus quitting. Heritability estimates for smoking persistence ranged from 27% to 70% and were greater for older than younger cohorts [99; 100; 101]. Madden et al. examined cross-cultural differences in the genetic risk of becoming a regular smoker and of persistence in smoking in men and women. They found strong genetic influences on smoking behavior, 46% for women and 57% for men, consistent across country and age group [102]. In a U.S. study, estimates of the genetic contribution to risk of becoming a smoker were 60% in men and 51% in women [103].

SMOKING DEPENDENCE

Of the numerous ingredients in tobacco smoke, nicotine is believed to be the primary cause of cigarette addiction [104]. Commercially available forms of nicotine-replacement therapy (NRT) increase cessation rates approximately 1.5- to 2-fold [105; 106; 107]. Yet, the fact that only a fraction of those who use such products succeed suggests that cigarette addiction depends on specific characteristics of cigarette smoking. It appears that the rapid delivery of nicotine via inhalation is a primary contributor to cigarette dependence [108]. Indeed, a district court judge found that major U.S. cigarette companies have designed their cigarettes to precisely control nicotine delivery levels and provide doses of nicotine sufficient to create and sustain addiction [109].

Active components of cigarette smoke affect many organ systems, but the effects on the CNS may be of most clinical importance due to its mediating role in dependence. Central effects of nicotine include electroencephalogram (EEG) desynchronization, with a shift toward higher frequency [110]. Studies have demonstrated that nicotine from cigarette smoke reduces global cerebral blood flow (gCBF), most markedly in the right hemisphere, and increases regional cerebral blood flow (rCBF) by more than 10% in the cerebellum, occipital cortex, and insula. Decreases in rCBF have been observed in such subcortical structures as the hippocampus, anterior cingulate, amygdala, and nucleus accumbens [111]. Positron emission tomography (PET) studies show that nasal nicotine administration increases cerebral glucose metabolism in the left inferior frontal gyrus, left posterior cingulate gyrus, left lateral occipitotemporal gyrus, left and right cuneus, and right thalamus, while it decreases glucose metabolism in the left insula and the right inferior occipital gyrus [112].

Further, the physiology of nicotine dependence has been characterized as biphasic; it stimulates the pleasure response in the brain and creates a relaxed state. As with cocaine, amphetamines, and morphine, addiction to nicotine is believed to result from increased release of dopamine in the nucleus accumbens. Nicotinic acetylcholine receptors are located throughout the CNS. Neurons located in the ventral tegmental area become more active with nicotine administration, leading to an increase in dopamine release into the nucleus accumbens [113]. Indeed, lesions to these pathways reduce rates of self-administered nicotine [114].

PSYCHOLOGICAL DEPENDENCE

Many smokers believe that smoking improves concentration, treats stress, and gives pleasure. These beliefs are false. The light-headed feeling that may accompany the act of smoking gives the smoker a false sense of pleasure or release. However, smoking actually causes a decline in physical and cognitive functioning. Additionally, a study by Ota et al. showed that nurses in Japan indulged in smoking as a result of the psychologic demands of their jobs, and this psychologic job demand was positively correlated with their Tobacco Dependence Screener score. The nurses associated stressful tasks with dysphoria, insomnia, anxiety, and other symptoms similar to that of nicotine withdrawal. To alleviate these symptoms, the nurses would smoke and become increasingly psychologically dependent on nicotine with each demanding occupational event [115].

HEALTH COMPLICATIONS RELATED TO SMOKING

PULMONARY COMPLICATIONS

Smoking severely compromises pulmonary function in a variety of ways, including causing infiltration of the airways with leukocytes. An imbalance among proteases, their endogenous

inhibitors, and local cytokine secretion in the lung leads to airway inflammation and alveolar destruction. Smokers also experience more acute lower respiratory illnesses. Smoking has been implicated in the development of malignant and nonmalignant lung disease, including COPD, bronchitis, influenza, emphysema, pneumonia, and lung cancer. Smokers are also shown to be at increased risk of intraoperative pulmonary complications and a wide range of postoperative complications. For example, a study of postoperative care revealed smoking, being older than 65 years of age, and a history of chronic lung disease increased the risk of unplanned intensive care admittance [116].

Chronic Obstructive Pulmonary Disease

Smoking is the main cause of COPD, which encompasses both chronic bronchitis and emphysema. Between 20% and 30% of smokers (or about 1 in 4) will develop COPD, and risk is determined largely based on genetic susceptibility coupled with age at smoking initiation [117; 118]. It is very rare in nonsmokers; at least 80% of deaths from this disease can be attributed to cigarette smoking. The risk of death from COPD rises concurrently with the number of cigarettes smoked. If smokers with COPD quit smoking while they are still young, an improvement in lung function can be expected. However, such improvement is not possible in older people, although after cessation further deterioration will run parallel to that of nonsmokers.

The age at which one begins smoking is important. Wiencke and colleagues discovered that smoking as an adolescent causes permanent genetic changes in the lungs and forever increases the risk of lung cancer, even if the smoker subsequently stops [119]. A Canadian community health survey conducted between 2000 and 2001 found that the risks for heart disease, COPD, and rheumatoid arthritis were far higher among people who began smoking as teenagers than among their nonsmoking peers. For COPD alone, teen smokers were three times more likely to develop the condition later in life than nonsmokers. Similarly, a retrospective cohort study of adult smokers suggests that women are particularly at risk of COPD if they start to smoke before 16 years of age [120].

Influenza

Upper respiratory tract infections are common, and tobacco smoke is a proven risk factor for bacterial infection. The link between influenza and smoking has been demonstrated both for adult smokers and children exposed to smoke-filled environments. According to Arcavi and Benowitz, influenza risk is higher and infections are more severe (e.g., more cough, phlegm production, breathlessness, and wheezing) in smokers versus nonsmokers. Apparently, the antibody response is depressed in cigarette smokers. Nonsmokers should also avoid SHS exposure to decrease the risk of contracting influenza [121]. In a study of Israeli military men, presence and severity of influenza was stronger in smokers than in nonsmokers. Of all smokers, 68.5% contracted influenza compared with 47.2% of nonsmokers, and 50.6% of smokers required bed rest or lost workdays compared with 30.1% of nonsmokers [122]. A 2018 study of patients older than 65 years of age showed that smokers had a higher rate of hospitalization due to influenza (47.4%) compared with nonsmokers (42.1%). In addition, the effectiveness of the influenza vaccine in preventing hospitalization was 21% among current and ex-smokers and 39% in nonsmokers [376].

Pneumonia

Smoking is associated with a significant increase in the relative risk of pneumonia and pneumonia-related hospitalization [123; 124]. Pneumonia is not only more common among smokers, it is much more likely to be fatal. Longitudinal studies have identified an increase in the mortality rate from pneumonia in smokers associated with dose-response [125]. In general, cessation of smoking is not associated with a decrease in hospitalization for pneumonia; however, patients without COPD and a greater than 10-year history of not smoking are at a decreased risk [124]. A 2013 study found that children exposed to SHS were four times more likely to develop lower respiratory illnesses, including pneumonia [126]. Proposed explanations of the increased risk for infection in active, passive, and former smokers include increased bacterial adherence, decrease of lung and nasal clearance, and changes in the immune response.

CARDIOVASCULAR COMPLICATIONS

Cardiovascular disease, defined as acute myocardial infarction (MI) and stroke, is strongly related to smoking and comprises 34% of smoking-related mortality; conversely, smoking yields 16% of cardiovascular-related mortality [62]. The relative risk of MI for smokers has been estimated at 2.88 for men and 3.85 for women, and the relative risk of stroke for smokers is estimated at 2.80. These estimates do not include the effects of passive smoking. Low-tar cigarettes and smokeless tobacco have similarly been shown to increase the risk of cardiovascular events among users in comparison to nonsmokers [127]. Cigarette smoking impacts all phases of atherosclerosis, from endothelial dysfunction to acute clinical events. Both active and passive cigarette smoke exposure predispose to cardiovascular events. The exact toxic components of cigarette smoke and the mechanisms involved in smoking that are related to cardiovascular dysfunction are largely unknown, but smoking increases inflammation, thrombosis, and oxidation of low-density lipoprotein cholesterol (LDL-C). Experimental and clinical data support the hypothesis that increased oxidative exposure may be a potential mechanism for initiating cardiovascular dysfunction. Research also suggests that small doses of toxic materials from tobacco smoke cause a nonlinear dose-response effect on cardiovascular function [128]. The risk for cardiovascular disease declines rapidly after smoking is ceased [129].

NEUROLOGIC COMPLICATIONS

Tobacco smoking is strongly related to atherosclerosis and chronic vascular disease. Atherothrombotic ischemic stroke, transient ischemic attack, and atherothrombotic origin symptomatic or asymptomatic peripheral arterial disease are all associated with a high risk of vascular death, MI, and stroke. Exposure to tobacco smoke is a noted risk factor of all these events. A positive association was found between cigarette smoking and subarachnoid hemorrhage (SAH), especially for aneurysmal SAH in women [130].

Evidence is emerging that suggests an association between the development of other neurologic diseases and smoking. A study by Riise et al. identified the risk of multiple sclerosis as higher among smokers than among those who never smoked [131].

Studies have shown that the amount of monoamine oxidase (MAO) is reduced by 30% to 40% in the brains of smokers, compared to nonsmokers or former smokers [132]. This reduction in brain MAO levels may result in an increase in levels of dopamine. It has been suggested that nicotine may have short-term protective actions against mechanisms that cause Alzheimer disease; however, the numerous toxins in cigarette smoke negate any benefit [133]. Though the risk for dementia is slightly higher in smokers, the relative risk for Alzheimer disease is unclear. A 2013 Alzheimer study using a mouse model found that smoking hastens disease onset, exacerbates amyloid pathology, and increases neuroinflammation and tau phosphorylation [133]. Further research is needed in order to better elucidate the risk.

CANCER

In the United States beginning in the early 1950s, a series of epidemiologic, biochemical, pathologic, and animal studies demonstrated a link between cigarette smoking and lung cancer. Tobacco smoking increases the risk of all histologic types of lung cancer. More than 80% to 90% of people who develop lung cancer are current or past smokers. However, not all smokers will develop lung cancer [134]. Cited reasons include the modification of lung cancer risk by previous respiratory disease. In comparison to nonsmokers, smokers are 23 times more likely to develop lung cancer if male and 13 times more likely if female. The risk of lung cancer increases directly with the number of cigarettes smoked and decreases when smoking is ceased. The most important parameter of smoking that affects lung cancer risk is the duration of smoking. Smoking low-tar cigarettes does not substantially reduce the risk of lung cancer [14].

Tobacco smoking is also causally linked to other types of cancer, including oral, oropharyngeal and nasal cavity, urinary tract, larynx, pancreas, esophageal, stomach, liver, cervix, colon, breast, endometrial, prostate, and leukemia. In most cases, the risk increases substantially with duration of smoking and amount of cigarettes/tobacco consumed. Similarly, alcohol in combination with tobacco greatly elevates the risk of many forms of cancer [14].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The U.S. Preventive Services Task Force recommends annual screening for lung cancer with low-dose computed tomography in adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.

(https://jamanetwork.com/journals/jama/fullarticle/2777244. Last accessed June 15, 2024.)

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.)

OSTEOPOROSIS

Smoking can lead to adverse long-term effects on bone health, rendering smokers prone to falls and fractures. Many smokers begin smoking during adolescence—a point in which bone mass is still being constructed; thus, smoking may hinder a person from reaching their maximum bone mass, leaving them fragile and prone to fractures with longer recuperation time [136]. Further, cigarette smoking has been shown to be a key risk factor for osteoporosis and unfortunately, menopausal women are at increased risk due to a loss of estrogen during this period of life. Giampietro and colleagues suggest that a genetic variation in interleukin 6 (IL6) and lipoprotein receptor-related protein 5 (LRP5) observed in smoking White women may confer risk for osteoporosis among smokers [137]. In a study of human-derived osteoblast-like cells and trabecular bone organ culture, Walker et al. demonstrated the presence of the α4 neuronal nicotinic acetylcholine receptor (nAChR) and found that nicotine modulates proliferation in a dose-dependent manner, upregulates c-fos transcription factor, and affects synthesis of osteopontin, a bone matrix protein [138].

PROBLEMS WITH CONCEPTION AND EMBRYONIC HEALTH

Women who smoke prior to pregnancy are more likely to experience a delay in conception and have about 30% higher odds of infertility [139]. Further, men who smoke are at increased risk of erectile dysfunction due to decreased bioavailability of nitric oxide and damage to peripheral nerves, the vascular epithelium, and structure of corporal tissue. Smoking may also affect the quality and mobility of spermatozoa [140; 141]. Ramlau-Hansen et al. report a dose-dependent relationship between smoking and sperm concentration, testosterone, luteinizing hormone (LH), and the LH/free testosterone ratio [142].

Success of assisted reproduction therapy (ART) is reduced among smoking couples. In a meta-analysis, Waylen and colleagues found that smokers undergoing ART (e.g., in-vitro fertilization, intracytoplasmic sperm injection, gamete intrafallopian transfer, zygote intrafallopian transfer) had lower odds of live birth per cycle (i.e., birth of one or more infants that show signs of life). They also observed lower odds of clinical pregnancy per cycle (i.e., a sonographically visible gestational sac in the uterus) and higher odds of spontaneous miscarriage and ectopic pregnancy when compared to nonsmokers undergoing the same treatments [143]. A retrospective study published in 2018 found that smoking has a negative effect on endometrial thickness on the day of the embryo transfer, resulting in lower rates of implantation and pregnancy [466].

If conception is achieved (with or without ART), maternal smoking during pregnancy increases the risk for adverse conditions including low birth weight, spontaneous abortion, placenta previa, abruptio placentae, preterm premature rupture of the membrane (PPROM), and overall poor outcomes [144; 145].

The miscarriage rate among mothers who smoke may be as high as 33% [146; 147]. This may be due to an increased syncytial necrosis and increased thickness of syncytio/cytotrophoblast membrane, as smoking appears to induce dysfunction of villous and invasive trophoblasts early in pregnancy. Additionally, maternal levels of estriol, estradiol, human chorionic gonadotropin, and human placental lactogen are lower in smokers than in nonsmokers [148]. All of these are markers of prenatal health and well-being.

COMORBID CONDITIONS

ALCOHOL ABUSE

There is a strong comorbidity between alcohol consumption and tobacco use. Drinkers are more likely to smoke than nondrinkers, and smokers are more likely to drink than nonsmokers [149]. In fact, smokers are 30% more likely to consume alcohol and 10 times more likely to develop alcoholism than nonsmokers. Between 80% and 95% of all persons with alcohol use disorder also smoke cigarettes, and 70% are heavy smokers who consume more than one pack per day [150]. A study examining an association between alcohol and tobacco, using a combination of short-term (1-year) and long-term (15-year) follow-up intervals, found that past-year alcohol and tobacco use disorders were associated not only cross-sectionally, but also prospectively. These associations were present even after controlling for age, gender, and race. Year 1 tobacco dependence prospectively predicted diagnosis with an alcohol use disorder (AUD) at year 2, and a baseline diagnosis of AUD increased the likelihood of diagnosis with tobacco dependence 15 years later. Having been diagnosed with tobacco dependence at year 1 predicted AUD persistence, and vice versa. These findings demonstrate the complex association between tobacco dependence and AUDs [151]. Similarly, a study examining the natural course of AUDs from adolescence to early adulthood found that daily smoking predicted future AUD when adolescent AUD and other disorders were controlled. It is possible that chronic smoking may contribute to alcohol tolerance, increasing alcohol consumption and metabolism [152].

In the instance of nonsmokers, data from a study by Romberger and Grant suggests that patterns of alcohol abuse would be similar in workers exposed to SHS; however, the severity of the alcohol abuse may be less pronounced [153].

RECREATIONAL DRUG USE

Smoking usually precedes recreational drug use. Among those who used both cigarettes and marijuana by the 12th grade, 65% smoked cigarettes before marijuana, and 98% of those who used both cigarettes and cocaine smoked cigarettes first. Apparently, the earlier a person uses tobacco, the more likely he or she will be to experiment with cocaine, heroin, and other drugs. More than half of those who start smoking before 15 years of age use recreational drugs in their lifetime, compared to only a quarter of those who do not start smoking until 17 years of age or later. Moreover, those who start smoking before 15 years of age are seven times more likely to use cocaine than those who never smoke. Also, heavy smokers are more likely to use marijuana or harder drugs. For example, young people who smoke more than 15 cigarettes a day are twice as likely to use any recreational drug and 16 times more likely to use cocaine than those who smoke less frequently. They are also 10 times more likely to use a recreational drug and 100 times more likely to use cocaine than those who never smoked. Even heavy users of smokeless tobacco are more likely to experiment with drugs. High school students who used smokeless tobacco 20 to 30 days per month were four times more likely to concomitantly use marijuana than nonusers, and almost three times more likely to ever use cocaine [150].

PSYCHIATRIC DISORDERS

Many smokers report a link between smoking and anxiety. Researchers at the National Institute on Drug Abuse hypothesized that impaired respiration and the detrimental effects of nicotine on blood vessels to the brain elucidate why those exposed to smoking are at an increased risk of developing anxiety disorders [154; 467].

Smoking is shown to be highly comorbid with such psychiatric disorders as major depression, panic disorder, and schizophrenia. Cigarette smoke has other psychoactive properties apart from nicotinic receptor stimulation. For example, it inhibits MAO, which is the enzyme responsible for breaking down the biogenic amine neurotransmitters norepinephrine, serotonin, and dopamine in the brain [155; 156]. Not surprisingly, the association between smoking and major depression is well established [157; 158; 159]. Reports of severe major depressive episodes after smoking cessation are also common, with the onset of depressive symptoms ranging from two days to six weeks after the initial abstinence from smoking [160; 161].

In some cases, depression was alleviated with the use of NRT or antidepressants; in others, depressive symptoms went away after a relapse to smoking [160; 162]. In a trial of smoking cessation using fluoxetine (30 mg), 7% of participants with a previous history of major depressive disorder (MDD) were diagnosed with major depressive episodes after a 10-week treatment, suggesting that a subset of smokers may be particularly at risk for developing MDD after smoking cessation [163].

In addition to relieving depressive symptoms or major depressive episodes associated with nicotine withdrawal, antidepressants may aid in long-term smoking cessation by substituting for the antidepressant effects of nicotine that help maintain smoking. They may also have a specific effect on neural pathways (e.g., MAO inhibition) or receptors (e.g., nicotinic-cholinergic receptor blockade) that underlie nicotine addiction. A 2013 Cochrane review assessed the efficacy of antidepressant medications to aid long-term smoking cessation. The majority (75) of the 90 randomized trials included in the review were of bupropion and nortriptyline. The reviewers found high-quality evidence that bupropion significantly increased long-term smoking cessation when used as the sole pharmacotherapy, and moderate-quality evidence (limited by the small number of trials and participants) that nortriptyline also significantly increased long-term cessation. The drugs' effectiveness for long-term smoking cessation was independent of their antidepressant effects, with efficacy similar to NRT [156].

Smoking could also be a risk factor for panic disorder [164; 467]. A disproportionate number of persons with panic disorder smoke cigarettes compared to the general population [165]. Mild-to-moderate nicotine dependence was associated with an 11% lifetime prevalence of panic disorder, a rate approximately 2.5 times greater than in persons with no nicotine dependence. Pohl et al. found that female patients with panic disorder had significantly higher smoking prevalence at the onset of their illness than did control subjects (54% versus 35%) and that smoking prevalence for the female patients was also significantly higher than for the control subjects (40% versus 25%) [166]. Male smoking rates did not differ between patients and control subjects.

Although the cause of this comorbidity remains controversial, several explanations have been offered: smoking promotes panic by inducing respiratory abnormalities/lung disease; nicotine produces the physiologic effects characteristic of panic by releasing norepinephrine; cigarette smoking is a form of self-medication for panic disorder; and/or a shared vulnerability promotes both conditions [167]. One study examined the effect of smoking cessation on the reduction of panic symptoms by monitoring the post-cessation abstinence status of 185 smokers. Abstinence was biochemically verified at weeks 1 and 2 and month 1. The severity of panic-relevant symptoms was self-reported by the participants at month 1 and month 3, post-cessation. The 80 participants (43.2%) who remained abstinent for one month, relative to the 105 (56.8%) who did not, demonstrated significant reductions in self-reported panic symptoms [168].

Smoking is also more prevalent in persons with schizophrenia, although reasons for its pervasiveness remain debatable [169; 170; 171]. Investigators have suggested that nicotine might temper positive or negative symptoms, and cigarette smoking is used as self-medication (e.g., to treat cognitive impairment and anhedonia) [171; 172; 173; 174]. Nicotine may also attenuate the adverse effects of neuroleptics, perhaps by reducing elevated blood levels after use of antipsychotic medications [128; 175; 176]. Weiser et al. examined the prevalence of cigarette smoking in apparently healthy adolescents later hospitalized for schizophrenia. The number of cigarettes smoked was significantly associated with the risk for schizophrenia. Compared to nonsmokers, adolescents who smoked 1 to 9 cigarettes per day were 1.38 times as likely to be hospitalized later for schizophrenia, and adolescents who smoked 10 cigarettes per day or more were 2.28 times as likely; the latter difference was statistically significant. The authors concluded that the higher prevalence of smoking in future schizophrenia patients might indicate that impaired nicotinic neurotransmission is involved in the pathophysiology of schizophrenia [177]. Bupropion has been found to increase smoking abstinence rates in smokers with schizophrenia [178]. Additionally, a number of medications that target nicotinic acetylcholine receptors have been tested or are in development, but further research is necessary to determine their clinical utility in the treatment of schizophrenia [174].

FETAL EXPOSURE

Maternal cigarette smoking before and during pregnancy adversely affects the health of both mother and fetus. However, analysis of data from the 2020 National Vital Statistics Systems (NVSS) indicated that 5.5% of pregnant women in the United States reported smoking during pregnancy; smoking during pregnancy is more common in rural and suburban America (approximately 14% and 12%, respectively) [452]. In addition to the effects on fertility and embryonic health discussed, maternal smoking before conception increases the risk of sudden infant death syndrome (SIDS), and smoking at the time of conception increases the risk of infants being born with cleft lip, with or without cleft palate [14; 180]. A 2010 study showed that as many as 8% of preterm deliveries, 7% of preterm-related deaths, 19% of term low-birth-weight deliveries, and 34% of SIDS cases in the United States were attributable to prenatal smoking [181]. Further, several studies indicate that the offspring of mothers who smoked during pregnancy are at elevated risk of developing nicotine dependence as adults [182; 183].

According to 2016 NVSS data, the prevalence of smoking during pregnancy was highest among women who were between 20 and 24 years of age (10.7%), followed by women 15 to 19 years of age (8.5%) and 25 to 29 years of age (8.2%). Among racial groups, the highest rates were found in non-Hispanic American Indian/Alaska Native women (16.7%%), followed by White (10.5%), Black (6.0%), Native Hawaiian/Pacific Islander (4.5%), Hispanic (1.8%), and Asian (0.6%) women.

Smoking rates were highest among those with a high school diploma or equivalent (12.2%), followed by those with less than 12 years of school completed (11.7%), and women with some college or an associate's degree (7.9%). Less than 1% of women with a bachelor's degree or higher reported smoking during pregnancy [179]. Rates of maternal smoking during pregnancy differ greatly between individual states, with West Virginia (25.1%) and Kentucky (18.4%) reporting the highest percentages, and the District of Columbia (2.6%) and California (1.6%) reporting the lowest. SHS exposure in infancy greatly increases the odds of respiratory tract infections, ear infections, and death from SIDS [14].

Ohida and colleagues performed cross-sectional surveys in Japanese obstetric clinics to investigate the effects of passive smoking on sleep disturbance during pregnancy [185]. Pregnant women exposed to passive smoking were likely to have insufficient sleep, difficulty initiating sleep, short sleep duration, loud snoring, or uncomfortable breathing. These experiences also occurred in pregnant women who were smokers.

Nicotine has a low molecular weight and high lipid solubility, allowing it to cross the placenta freely and accumulate in amniotic fluid. In animal models, nicotine could be identified in fetal tissues as early as five minutes following maternal injection [186; 187]. Because less than 5% of nicotine binds to human plasma proteins, the majority of the administered dose is available to equilibrate with fetal circulation [188]. Studies in humans showed that nicotine is readily transferred to the fetal compartment throughout pregnancy, with accumulation in placental tissue and amniotic fluid [189]. Apparently, a significant amount of nicotine is retained by the placenta and may later transfer to fetal and maternal circulation, thus prolonging the effect of nicotine on the fetus [188].

Acetylcholine causes dilation of blood vessels and maintains placental blood flow by the activation of endothelial muscarinic receptors. Nicotine blocks acetylcholine-facilitated amino-acid transport, depressing diffusion of amino acids and other nutrients from the trophoblast into placental circulation. Maternal smoking actually leads to trophoblast apoptosis and thickening of the trophoblast basement membrane [190; 191]. Further, CO from tobacco smoke crosses the placenta by passive diffusion, leading to increased carboxyhemoglobin in umbilical cord blood and placental hypoxia. The resultant hypoxia causes fetal growth retardation and alteration in the physiologic development of organs and tissues [192].

PHARMACOKINETICS AND DYNAMICS

Among pregnant smokers, maternal levels of cotinine correlate better with outcome measures such as birth weight than the number of cigarettes smoked per day [193]. Cotinine can accumulate in fetal compartments as early as 7 weeks' gestation in both active and passive smokers [194]. Of note, the half-life of nicotine is three to four times longer in newborns than in adults, whereas the half-life of cotinine is similar in newborns and adults. The prolonged elimination of nicotine, but not of cotinine, in the newborn compared with that in the adult may be a result of different newborn cytochrome P450 2A6 (CYP2A6) enzymatic substrate specificity, low CYP2A6 activity with another enzyme that is primarily responsible for cotinine metabolism, or differences in tissue distribution [195]. Also, pregnancy is well known for affecting metabolism of some drugs and may contribute to higher or lower clearances compared with the nonpregnant state [196]. Indeed, metabolic clearance of both nicotine and cotinine are substantially increased during pregnancy, resulting in a marked decrease in the half-life of cotinine. The mechanism for such increase in metabolic clearance is not known. It is possible that nicotine and cotinine clearances are accelerated by faster oxidation via CYP2A6 and faster glucuronide formation. Although nicotine and cotinine share the same metabolizing enzymes, their increased clearances may occur by different physiologic mechanisms. Nicotine is a rapidly cleared drug with a high affinity for CYP2A6, and the rate of clearance is primarily controlled by liver blood flow. Cotinine is a slowly metabolized chemical, with a low affinity for CYP2A6 relative to nicotine. The level of CYP2A6 in the liver, which is markedly elevated during pregnancy, primarily determines the rate of cotinine metabolism. A substantial increase in the percentage of nicotine and cotinine excreted as their glucuronide conjugates is also observed in pregnancy, but there is no increase in the percentage of 3'-hydroxycotinine excreted as a glucuronide. This suggests an acceleration of nicotine and cotinine metabolism via the *N*-glucuronidation pathway, but no effect on hydroxycotinine metabolism by the *O*-glucuronidation pathway. Also, the profile of nicotine and its metabolites in urine is altered during pregnancy. The excretion of nicotine is substantially decreased, and despite large differences in plasma cotinine concentration during smoking, there is no difference between the daily dose of nicotine absorbed from cigarette smoking during and after pregnancy [197].

NEUROLOGIC COMPLICATIONS

Fetal nicotine exposure can result in permanent abnormalities of the dopaminergic regulation of the brain [198]. These effects can occur even at low nicotine doses and lead to a greater nicotine dependence [182]. Unlike in mature organisms, where stimulation of a target cell elicits only a short-term response, receptor stimulation in the developing systems interacts with the genes controlling cell differentiation, permanently altering the cells' responsiveness. Nicotine exposure to the prenatal brain may also prematurely stimulate the shift from proliferation to differentiation; thus, nicotine may act as a cholinergic signal, mimicking trophic effects of acetylcholine. Because of the close regulatory association of cholinergic and catecholaminergic systems, adverse effects of nicotine involve multiple transmitter pathways and influence not only the immediate developmental events in the fetal brain but also the eventual programming of synaptic competence. Therefore, defects may appear after a prolonged period of apparent normality, leading to cognitive and learning defects that appear in childhood or

adolescence. Similar modifications occur in peripheral autonomic pathways, leading to increased susceptibility to hypoxia-induced brain damage and perinatal mortality [199]. These changes are especially prominent in tissues rich in nicotinic cholinergic receptors, such as the brainstem [200].

Prenatal exposure to nicotine produces alterations in tegmental nuclei related to the following [201]:

- Cardiopulmonary integration (nucleus tractus solitarii, parabrachial complex)
- Regulation of arousal, attention, and rapid eye movement (REM) sleep (mesencephalic and pontine reticular formation)
- Somatic motor control (paramedian pontine and medullary reticular formation)
- Tongue and upper airway regulation (hypoglossal nucleus)

Autonomic deregulation could explain the inhibition of some homeostatic reflexes seen in infants exposed to tobacco smoke, including a deficiency in arousal responsiveness to hypoxia or hypercapnia [202]. Roy et al. evaluated cellular morphology and regional architecture in the juvenile and adolescent hippocampus and the somatosensory cortex in rats prenatally exposed to nicotine. They found a substantial decrease in cell size in the hippocampal CA3 region and dentate gyrus, with corresponding decrements in cell layer thickness and increments in cell packing density. Smaller, transient changes were seen in CA1. There was a reduction in the proportion of medium-sized pyramidal neurons in layer five of the somatosensory cortex and an increase in the proportion of smaller, nonpyramidal cells. All regions showed elevated numbers of glia. These data demonstrate that prenatal nicotine exposure compromises neuronal maturation, leading to long-lasting alterations in the structure of key brain regions involved in cognition, learning, and memory [203].

PULMONARY COMPLICATIONS

Fetal growth and duration of gestation are the major factors affecting lung development [204]. Intrauterine influences that retard fetal weight gain may irrecoverably restrict the growth of the airways, with consequences persisting throughout the individual's life span. Fetal exposure to nicotine is associated with several abnormalities in lung growth. In animal studies, nicotine has been shown to directly interact with nicotinic acetylcholine receptors in pulmonary vessels, altering connective tissue expression and producing vascular structural alterations [205]. Furthermore, maternal nicotine exposure results in larger alveolar volumes and suppresses alveolarization in the lungs of the offspring of rats, reducing the surface potentially available for gas exchange [206; 207]. Human smokers have a high rate of poor perfusion patterns, suggesting that smoking during pregnancy may compromise uteroplacental blood flow and contribute to poor fetal development [208; 209].

CARDIOVASCULAR COMPLICATIONS

Maternal smoking during pregnancy poses severe risks to the developing fetal heart. Nicotine alters cardiac cell differentiation to increase the cellular injury caused by hypoxia [210]. Prenatal nicotine exposure interferes with the ability of neonatal adrenal glands to secrete catecholamines in response to hypoxia [200]. Given that the neonatal heart lacks functional sympathetic innervation, there is virtually a complete dependence on circulating catecholamines secreted by the adrenal medulla to maintain heart rate response to hypoxia. Nicotine exposure reduces the number of cardiac ß-adrenergic receptors, magnifying functional consequences of impaired catecholamine release [211]. The resultant impaired cardiac function can lead to cardiovascular collapse, subsequent brain damage, and/or death during delivery [212; 213].

Adenosine diphosphate (ADP) is a major factor in determining electrical stability of myocytes, because the longer the action potential, the higher the likelihood of abnormal cardiac activity [214]. It is possible that a component in smoke temporarily disables electrical properties of ventricular myocytes, rendering the ventricular muscle more susceptible to developing arrhythmias [215].

Fetuses exposed to smoke also manifest an increase in cardiac volume growth between 23 and 27 weeks' gestation [216; 217]. This could be attributed to either an exaggeration of normal cardiac growth patterns or a compensatory response to an increase in upper body growth at the time.

LOW BIRTH WEIGHT AND SMALL FOR GESTATIONAL AGE

Infants born to mothers who smoke weigh less than other infants (independent of maternal body mass index), and low birth weight (<2,500 grams) is a key predictor for infant mortality. Effects of maternal smoking during pregnancy on infant birth weight have been recognized since 1957; nevertheless, smoking remains the most hazardous factor affecting a newborn's weight, even at present [218; 219; 220]. Similar to earlier studies, Bernstein and colleagues report that maternal third-trimester cigarette smoking is one of the strongest predictors of low birth weight. This study is thought to be the first to accurately assess maternal smoking levels, and startlingly, they purport that there is an estimated 27 g reduction in birth weight per cigarette consumed each day during the third trimester, or roughly twice the amount previously shown [220]. Another study found that 11.5% of infants born to women smoking less than six cigarettes daily had low birth weight [221]. Taken together, these studies demonstrate that there is not a safe level of smoking during pregnancy [221; 222]. Additionally, Aagaard-Tillery et al. reported that tobacco-exposed infants were small for gestational age regardless of maternal body mass index or pregnancies complicated by diabetes or hypertension [223].

A study examining the effect of prenatal smoke on a fetus in midgestation identified greater early gestational upper-body growth with preferential growth of head dimensions, upper limb length, and abdominal circumference with smoke exposure. This was followed by decreases in biparietal dimensions of the head, abdominal diameter, and distal limb length. Data from the late gestation period revealed cranial dolichocephaly, proportionally longer upper limbs, and legs with relatively reduced tibias, indicating that smoke exposure altered the growth rate of individual body segments [216]. It is possible that during hypoxia, blood supply to the lower limbs and internal organs is reduced in order to preserve brain metabolism [224]. Retardation of limb growth by 32 weeks could be due to diminished oxygen availability for distribution to distal tissues. The tibia, being one of the last consumers in the fetal nutrient distribution food chain, is therefore regarded as a good marker of available oxygen resources [216].

MIDDLE EAR DISEASE

Passive smoke exposure is independently associated with an increased risk of otitis media [222; 225; 226]. Though the immediate complications of otitis media are significant, one must also consider the lasting complications including an increased prevalence of speech and language difficulties, attention disorders, and learning difficulty [226]. The mechanism by which cigarette smoke causes otitis media is currently unknown. Histologic changes in fetal alveolar and bronchial epithelium lend support to a contemporary theory that purports that fetal cigarette smoke exposure may interfere with the development of the middle ear and eustachian tube epithelium. An alternative theory proposes that passive smoke-related immune system depression allows for opportunistic middle ear infections [226].

CANCER

One of the potentially negative effects of smoking during pregnancy is exposure of the fetus to carcinogens [227; 228]. The potent tobacco-related carcinogen 4-aminobiphenyl has been shown to cross the human placenta and bind to fetal hemoglobin [229]. Two metabolites of the tobacco-specific transplacental carcinogen NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronide (NNAL-Gluc), were detected in the urine from newborns of mothers who smoked cigarettes during pregnancy [144]. Studies relating childhood and in utero cigarette exposure to brain tumors and leukemia have been inconsistent in their findings [230]. A meta-analysis of the association between exposure to maternal tobacco smoke during pregnancy and cancer in childhood found a small increase in risk of all neoplasms (based on 12 studies) but not of specific neoplasms such as leukemia (based on 8 studies) and CNS tumors (based on 12 studies) [231].

OSTEOPOROSIS

Maternal smoking has been shown to modulate bone mineral acquisition for the fetus, which may lead to increased risk of osteoporosis later in life [232].

PSYCHIATRIC DISORDERS

Previous studies have reported an association between maternal smoking during pregnancy and behavioral problems such as hyperactivity and decreased attention span. The association with behavioral problems has been shown in investigations of hyperactive children and controls, sibling studies in which the mother smoked in one pregnancy but not in the other, and in neuropsychologic evaluations of children of smokers and nonsmokers using tests of sustained vigilance and attention [233; 234; 235; 236]. Naeye and Peters found that hemoglobin levels in neonates increased with the number of cigarettes smoked by the mother during pregnancy and that children who were more active or had shorter attention spans had significantly higher hemoglobin levels [235]. Further, early secondhand exposure to nicotine as a child via maternal smoking during pregnancy shows an association with offspring attention deficit hyperactivity disorder (ADHD) symptoms [237; 238]. Evidence also supports a statistical association between prenatal smoking and increased risk for antisocial outcomes in offspring. Maternal smoking during pregnancy has been shown to be associated with a significant increase in externalizing behavior (tendency to seek controversy, aggressive, hyperactive) but not internalizing behavior (withdrawn, depressed, anxious) problems [239]. Similarly, maternal smoking during pregnancy has been shown to have an adverse effect on the child's negativity [240]. In a sample of 99 children 2 years of age, maternal smoking was identified as a significant predictor of childhood negativity, independent of demographic factors, perinatal factors, maternal personality attributes, and the mother-child relationship. Behavior problems associated with in utero exposure to SHS seem to continue into childhood and young adolescence, demonstrated by increased risk for ADHD, conduct disorders, criminality, and substance abuse [241]. An 18-year epidemiologic study of 1,265 New Zealand children identified that maternal smoking during pregnancy contributed to risk of higher psychiatric symptom rates for conduct disorder(s), alcohol abuse, substance abuse, and depression [242; 243].

PASSIVE SMOKING EFFECTS ON CHILDREN

It is possible that SHS exposure during childhood may be potentially more hazardous to neurodevelopment than in utero exposure to maternal smoking. Young children have higher ventilation rates, meaning they receive higher levels of SHS for the same duration and level of external exposure [244]. Passive smoking is believed to increase the prevalence of sudden infant death syndrome (SIDS); exacerbate asthma symptoms; interfere with cognition and behavior; increase cancer risk; and cause respiratory tract illness [226; 245; 246]. Breastfed infants with a smoking or snuff-taking mother are exposed to nicotine in breast milk, with a mean intake of nicotine of 7 mcg/kg per day [247]. Older children experience decreased physical fitness and are susceptible to tobacco-related illnesses just as adult smokers are.

Aside from adverse health effects due to SHS exposure, parental smoking is also positively correlated to their offspring's smoking as adolescents and adults. Counseling parents on the adverse health effects of SHS on children has been shown to dramatically reduce their children's subsequent cigarette smoke exposure [6; 246]. Smokers should be encouraged to smoke outside their homes and minimize SHS exposure to their children [248]. However, studies have shown that, though smoking outdoors decreases SHS exposure, children of parents who smoke outdoors still have higher prevalence of ear infections and respiratory symptoms than children of nonsmokers [249].

The American Heart Association recommends that all children at increased risk for complications be screened for smoke exposure and provided with counseling on lowering exposure and quitting. The nicotine patch or gum can be considered if counseling is ineffective.

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Level of Evidence: A (Well-designed randomized controlled trials or diagnostic studies performed on a population similar to the Guidelines' target population)

NEUROLOGIC EFFECTS

Prenatal and perinatal exposure to SHS adversely affects neurobehavioral development. Evidence now supports the notion that tobacco-exposed infants are more excitable and hypertonic, require more handling, and show more stress and abstinence signs than infants not exposed to tobacco. Symptoms are particularly noteworthy in the CNS, gastrointestinal system, and visual areas [250]. The presumed neurobiologic effect of SHS is altered brain development resulting from fetal hypoxia, due to either nicotine acting to reduce blood flow to the fetus, or possibly CO, which produces higher levels of carboxyhemoglobin. Nicotine may also target specific neurotransmitter receptors in the fetal brain to discoordinate the events of cell replication, differentiation, and synaptic development in the brain. Nicotine is thought to disrupt brain development via cholinergic mechanisms. In rats, exposure to nicotine alone has been shown to result in a significant increase in acetylcholinesterase (AChE) activity in the brainstem and midbrain. A significant increase in ligand binding to nAChR has been observed in the brainstem and cortex following exposure to nicotine. This suggests that exposure to nicotine may impair neurobehavioral performance and affect the cholinergic pathways [251].

In another study, postnatal SHS reduced hindbrain (comprising the pons and medulla oblongata) DNA concentration, increased the protein-to-DNA ratio, and reduced the body weight of exposed rats. These data suggest that postnatal exposure to SHS affects the hindbrain, a region that undergoes significant postnatal growth, by reducing the total number of cells and by increasing cell size. The authors concluded that, despite preserved hindbrain weight, the effects of postnatal exposure to SHS might result in neurologic dysfunction [252]. This study provided clear biologic evidence for an alteration of brain development due to postnatal, but not prenatal, SHS exposure. Interestingly, although gross dysmorphology is demonstrable in the animal brain by SHS exposure to nicotine, brain structures are not grossly abnormal when examined later in adolescence or adulthood [203]. However, longer-lasting changes in morphology are noted in the hippocampus and somatosensory cortex in the form of decreased cell size and elevated numbers of glia. In considering synaptic function, several neurochemical studies have identified multiple biochemical markers of cell injury that indicate prenatal nicotine exposure damages the developing brain [253; 254].

CARDIAC COMPLICATIONS

Nicotine exposure causes myocyte cell damage in newborns, reduced platelet activation, increased resting sympathetic nerve activity, and hypertension. In rats, exposure to SHS during the neonatal period resulted in abnormal vasoconstrictor and vasodilator responses and smooth muscle dysfunction [255]. Abnormalities of endothelial cell function were found in rabbits exposed to SHS for 3 to 10 weeks [256]. Exposure to SHS also appears to directly affect endothelial function in children by means of a dose-dependent decrease in the bioavailability of nitric oxide [257]. Exposure to SHS also caused left ventricular hypertrophy in rabbits [258]. SHS exposure in childhood reduces high-density lipoprotein levels [259]. In addition, adolescents exposed to their parents' smoke show depressed levels of high-density lipoprotein cholesterol (HDL-C), suggesting that SHS exposure may accelerate atherosclerotic change and place children at increased risk for the premature development of coronary artery disease [260; 261].

SIDS

SIDS occurs within the first year of life and is a significant cause of infant mortality, with an estimated 3,400 deaths in the United States annually [262]. SIDS is a diagnosis of exclusion, and etiology is presently unclear. Various risk factors have been suggested including prone sleeping position, sex, age, birth weight, parental cigarette smoking, maternal substance abuse, bed sharing, soft bedding, and overheating [262; 263]. Matturi et al. found evidence supporting an association between maternal smoking and SIDS. Specifically, CO from cigarette smoke forms carboxyhemoglobin, leading to brain hypoxia. This lack of oxygen inhibits normal brain development of the arcuate nucleus and normal brain function in the locus coeruleus and arcuate nucleus. These abnormalities could potentially affect control of the respiratory and cardiovascular systems, resulting in sudden unexplained infant death. Matturi et al. concluded that the most preventable risk factor for SIDS is maternal smoking during pregnancy [264]. Zhang et al. concluded that the association between maternal smoking and elevated SIDS risk is dose-dependent and significantly increased in infants

who co-sleep with smoking mothers [265]. Another study that sampled pericardial fluid in SIDS cases found that 70% had elevated levels of cotinine [266].

PULMONARY COMPLICATIONS

Children with smoking parents demonstrate higher frequencies of common respiratory symptoms including cough, phlegm, asthma, breathlessness, and wheeze. Parental smoking inhibits lung growth and function during childhood [267; 268; 269; 270]. One study assessed the pulmonary function of 80 healthy infants soon after birth and found significantly reduced pulmonary function in infants whose mothers had higher urine cotinine concentrations [271]. Another study demonstrated an association between in utero nicotine exposure and variable DNA methylation in fetal lung and placental tissues, suggesting that this variation may have a role in the fetal origins of chronic diseases [272].

Cough/Wheeze

Both past and current SHS exposure has been shown by multiple studies to cause cough and wheeze in children. Joad et al. worked with guinea pigs to establish the mechanism by which air pollutants, particularly SHS, causes cough. Secondhand smoke modifies afferent sensory fibers (specifically C-fibers and rapidly activating receptors) in the lungs and airways, thereby activating a neurally controlled cough mechanism. The vagus nerve receives input from the afferent sensory fibers, which is modified by interneurons in the nucleus tractus solitarius (NTS). A few additional modifications of the efferent activity occur in the brain stem. Cough occurs when the efferent signal modifies input to the respiratory muscles involved in inspiration and expiration. Wheeze occurs with bronchoconstriction and mucus secretion, which can be caused by locally released neurokinins or parasympathetic fibers synapsing on airway ganglia [64].

Asthma

Asthma is a chronic inflammatory disease, often with an initial onset in childhood. An association has been established between exposure to passive tobacco smoke and pediatric asthma development, while a causal relationship has been shown between exacerbated pediatric asthma and environmental tobacco exposure [273; 274]. Cigarette smoke causes an "exaggerated bronchoconstrictor response" in asthmatics, leading to an increase in severity and frequency of acute asthma attacks as well as asthma-related hospitalizations [275]. Studies have shown a decreased respiratory drive and hypoxic ventilatory response in infants of smoking mothers [247]. Exposure to nicotine for the full gestation produced an increased risk of depressed hypoxic ventilatory response in rats [18]. Parents of asthmatic children should be strongly cautioned that smoke exposure is likely to dramatically worsen their child's asthma [276; 277].

DENTAL CARIES

Each year, several billion dollars are spent treating pediatric dental caries in the United States. Dental caries are an oral infectious disease caused by *Streptococcus mutans* colonization and subsequent lactic acid production leading to dental decay. In addition to poverty, passive smoking is a substantial risk factor for developing dental caries. The reason for an increased prevalence of dental caries in children of low socioeconomic status is unclear. However, as poor children are more likely to be exposed to SHS, it has been suggested that environmental tobacco smoke exposure may help explain the increased dental decay in this particular population. Environmental tobacco smoke is considered a causal factor for dental caries in primary but not in permanent teeth. Mechanisms for the role of cigarette smoke in the development of pediatric dental decay include nicotine promotion of bacterial growth; immunosuppression from environmental tobacco smoke; decreased levels of vitamin C leading to increased bacterial growth; passive smoking-related saliva reduction, which impairs the natural defense against bacteria-related acid production; and a general increase in inflammation [278].

VITAMIN DEFICIENCY

Vitamin C (ascorbic acid) deficiency is common among active smokers due to both increased metabolism and decreased dietary consumption [68]. Cigarette smoking-induced oxidant damage is caused by both the immune system's inflammatory response and free radicals in cigarette smoke. Vitamin C and other antioxidants play an important role in preventing oxidant-induced damage.

Studies have supported a dose-dependent inverse relationship between environmental tobacco smoke exposure and ascorbic acid and beta carotene concentrations [68; 279]. A 2011 study found that children with no SHS exposure had higher levels of vitamin A, C, and E, beta carotene, and folate (controlling for dietary and supplement intake) than children with either moderate or high SHS exposure [279]. A lower concentration of these key nutrients was associated with higher cotinine levels. Vitamin B6, B12, and D levels were not found to be significantly affected.

RESULTANT SYMPTOMS IN ADULTHOOD

The relationship between childhood passive smoke exposure and resultant health consequences in childhood has been firmly established. There is less known about the long-term respiratory effects of childhood passive smoke exposure. David et al. studied Chinese adults from the Singapore Chinese Health study who were exposed to cigarette smoke as children but never actively smoked, thereby eliminating active smoking as confounding bias often found in similar studies. They found an association, independent of adult SHS exposure, between childhood environmental tobacco smoke exposure and chronic dry cough and phlegm production. Other findings included a lack of an association between childhood SHS exposure and asthma or chronic bronchitis. Also, they found low-fiber

predisposed patients to respiratory maladies [280]. One study found a 50% increase in adult-onset cancer for children whose fathers smoked, and the risk of hematopoietic cancer increased when both parents smoked [281].

Peppone et al. reported that never-smoking women who grew up with a smoking parent may have more difficulty becoming pregnant. Those exposed to SHS regularly in childhood and adulthood were 39% more likely to have suffered a miscarriage or stillbirth and 68% more likely to have trouble conceiving when trying for more than one year [282]. Further, among women exposed to environmental tobacco smoke in youth undergoing ART between 1994 and 1998, there was decrease in implantation rate and increased odds of spontaneous abortion [65].

In a study by Strohsnitter et al., early menopause was more likely to occur in never-smoking women exposed to maternal cigarette smoke. They attribute this association to smoke's effects on follicle production in utero [283].

PASSIVE SMOKING EFFECTS ON ADULTS

The International Agency for Research on Cancer (IARC) Working Group concluded that secondhand tobacco smoke is carcinogenic to humans [284]. Complications of exposure to SHS include adverse effects on the pulmonary, cardiovascular, and neurologic systems as well as increased risk for cancer and fibroblast changes.

OCCUPATIONAL EXPOSURE

Occupational exposure to SHS affects the health of countless employees worldwide. Workplace exposure is highly influenced by the type of smoking policy in the workplace. Airborne nicotine is present, often in excessive concentrations, in various job settings due to variable public smoking laws [285; 286]. Local and state regulation of smoking in public places was instituted in response to data published by the American Society of Heating, Refrigerating and Air Conditioning Engineers (ASHRAE). These standards assert that satisfactory indoor air quality cannot be maintained if smoking is allowed indoors, even with additional ventilation and air-cleaning devices [287]. Several studies have shown that smoke-free workplace policies decrease exposure of nonsmoking employees to SHS at work, while increasing rates of smoking cessation and decreasing the number of employees who smoke [14; 288; 289; 290; 291]. Policies that are less restrictive are associated with higher levels of sustained tobacco use among employees [290]. Policies that make indoor workplaces smoke-free result in improved worker health [290; 292]. For example, smoke-free polices in the hospitality industry have been shown to improve health among bar workers, who are often heavily exposed to SHS in the absence of such policies [184; 290; 293].

Studies have shown that segregating smokers and nonsmokers within the same airspace reduces SHS exposure to nonsmokers but does not eradicate it. One such study, in smoking-segregated restaurants in Albuquerque, New Mexico, showed levels of nicotine in nonsmoking sections approximately equal to those found in smoking sections [294].

SHS remains an issue for those employed in some casinos, bowling alleys, restaurants, lounges, and bars [295]. These work environments can contain high concentrations of airborne nicotine in the air if there is a lenient smoking policy. One study found that male blue-collar workers are exposed to significantly more SHS than their counterparts in management/professional occupations [296]. Also, on average, blue-collar smokers smoke more heavily than white-collar smokers [296]. Interestingly, female blue-collar workers are far less likely to smoke than women in management/professional occupations [296]. However, women's SHS exposure is approximately equal regardless of occupation, and SHS exposure is lowest for female service industry workers.

In 1986, the National Academy of Sciences warned, "SHS (also called environmental tobacco smoke) is a hazardous substance and is the most frequent source of complaint about aircraft air quality. Because of the high concentration of SHS generated in the smoking zone, it cannot be compensated for by increased ventilation in that zone" [297]. The area, volume, and ventilation rate per smoker on an aircraft is the smallest of any workplace setting. However, essentially all airlines now prohibit smoking on their planes.

Overall, exposure to SHS in different microenvironments is based on the strength of the active source, the ventilation system, and the presence and effectiveness of air-cleaning devices. Personal SHS exposure is also affected by age, gender, and race. Constant exposure to SHS at workplaces leads to various complications to the exposed workers.

HEART DISEASE

SHS is estimated to cause 5% to 30% of premature deaths from heart disease each year in the United States among nonsmokers [14; 298]. A key difference between the effects of smoking on the risk of cancer compared with the risk of heart disease is that the effects on cancer develop slowly, whereas the effects of smoking on the cardiovascular system occur rapidly. Passive smoking has been shown to cause atherosclerosis in both animal and human models, increase platelet aggregation, and increase myocardial oxygen demand. Multiple epidemiologic studies have consistently found an increased relative risk of cardiac events in nonsmokers with regular SHS exposure [299; 300]. Investigators demonstrated through experimentation that 30 minutes of exposure to SHS compromised the endothelial function in coronary arteries of nonsmokers so that the endothelial response of nonsmokers was identical to that of routine smokers [301].

The CDC asserts that people at risk for heart disease should avoid SHS because it can increase one's risk of acute MI. A study was conducted to verify this assertion and concluded that smoking bans at public working places correlate with a reduced morbidity from heart disease [302]. Researchers have suggested that platelet activation, endothelial dysfunction, and

broad inflammation may have some relevance [303]. Another theory states that even light exposure to smoke concomitantly restricts blood vessels and allows for blood clotting. This combination raises the risk for MI.

Atherosclerosis

Atherosclerosis, a chronic inflammatory atheromatous disease characterized by focal, noncircumferential, and (most often) proximal plaques, is a major underlying cause of cardiovascular disease, which continues to be the leading cause of death, accounting for 874,613 deaths in the United States in 2019 [304]. Monocytes play a key role in the pathogenesis of atherosclerosis. Monocytes migrate from the blood to the subendothelial space beneath injured endothelial cells, where they differentiate into macrophages. These subendothelial macrophages readily take up oxidized LDL, becoming "foam cells." Collections of "foam cells" are dubbed "fatty streaks" and may first appear in the aorta at 10 years of age. Fatty streaks are precursors to atherosclerotic plaques. Such plaques are advanced lesions characterized by the accumulation of lipid-rich necrotic debris and smooth muscle cells [63; 305]. Triggers of endothelial cell injury include hyperlipidemia; bacterial or viral infection; oxidative stress through abnormal regulation of reactive oxygen species, hypoxia, turbulent blood flow, and shear stress; and environmental irritants, such as tobacco smoke [306].

Yuan et al. exposed transgenic human apoB-100 mice to sidestream whole smoke (SSW) (a major component of SHS) in order to study the effects of SHS on atherosclerosis. The transgenic mice received SHS exposure comparable to SHS exposure a nonsmoker would receive from a typical smoking housemate. They found a decrease in plasma HDL-C levels; a decrease in the ratio between HDL-C and triglyceride; and a decrease in ratio between HDL-C and total cholesterol. Yuan et al. noted increased lipid accretion in the aorta, heart vessels, and hepatocytes corresponding to the noted blood lipid profile alterations. Furthermore, they found increased levels of monocyte chemoattractant protein-1 (MCP-1) in blood, heart tissue, and aortic tissue. Increased numbers of macrophages were noted in arterial walls. This finding was significant as MCP-1 is a chemokine that attracts monocytes to the damaged subendothelial cells in the process of plaque formation. Decreased adiponectin monomer levels were noted in the smoke-exposed mice [63]. Adiponectin is an adipocyte-specific plasma protein with potential anti-atherogenic properties. In vitro, adiponectin suppresses the endothelial inflammatory response, the proliferation of vascular smooth muscle cells, and the transition of macrophages to foam cells [307]. Finally, based on examination of the cytokine profile, Yuan et al. determined that cigarette exposure caused a permanent pro-inflammatory state; the normal adaptive response (i.e., initial pro-inflammatory Th1 type cell-mediated response to a Th2 mediated immune response) did not occur [63].

Coronary Heart Disease

A strong association between active smoking and coronary heart disease has been well established, and one study found a 50% to 60% increase in risk for coronary heart disease development in passive smokers [308; 309]. Active and passive smoking are known to [310]:

- Increase the incidence and frequency to cardiac arrhythmias
- Decrease the oxygen-carrying capacity of blood
- Increase the incidence of coronary artery spasm
- Promote atherosclerosis, thereby increasing the risk of cardiovascular disease
- Increase the incidence and tendency for thrombosis

The relationship between SHS and coronary heart disease is supported by a study that shows exposure to SHS is associated with increased inflammatory markers, including higher white blood cell counts and levels of C-reactive protein, homocysteine, fibrinogen, and oxidized LDL-C [311]. The intensity of inflammation markers was proportional to the number of years of reported exposure to SHS. Furthermore, subjects with only occasional SHS exposure also experienced increased levels of inflammatory markers, showing that even low SHS exposure is a significant concern. Increased coronary risk is mechanistically mediated by increased platelet aggregation, reduced oxygen uptake and exercise capacity, accelerated lipid peroxidation, and endothelial damage by SHS [312; 313; 314]. Passive smoke causes arteriosclerosis by altering cholesterol concentrations or by accelerating lipid peroxidation via reductions in serum antioxidant defense [315].

Many elements of tobacco smoke, including CO, nicotine, and polycyclic aromatic hydrocarbons, contribute to the damaging effects on the cardiovascular system. Studies of the effects of tobacco smoke on platelet sensitivity suggest that nicotine is not the sole cause of increased aggregation. Burghuber et al. compared the sensitivity of platelets to the antiaggregatory action of exogenous prostacyclin (PGI2) in nonsmokers and smokers exposed to SHS for 20 minutes. No change was observed in the smoking subjects' platelet sensitivity to PGI2 after SHS exposure, but the smokers' platelets were significantly lower than that of the nonsmoking subjects' before SHS exposure. The nonsmoking subjects experienced significant changes in sensitivity to PGI2 with reported platelet sensitivities matching those of smokers after SHS exposure [316]. However, another study by Benowitz et al. showed that smokers and abstinent smokers with nicotine patches differed significantly in platelet activity despite similar nicotine levels [317]. Thus, nicotine is not the only component of tobacco smoke that mediates increased platelet aggregation.

A British regional heart study examined 4,729 men 40 to 59 years of age and found a 50% to 60% increase in coronary heart disease caused by exposure to SHS [309]. This study is significant because most studies on the relationship between

SHS and coronary heart disease either show significant risk increases or only show modest risk increases. Whincup et al. used cotinine measurements to determine passive exposure to smoking. This study noted that although high cotinine levels were associated with an excessive risk of coronary heart disease, they showed little association with the risk of stroke. Whincup et al. offered an explanation for the underestimated association between serum cotinine and coronary heart disease, in that the association tends to decrease over long follow-up periods since assessment of exposure. Finally, this study suggested that risks associated with passive smoking are widespread among nonsmokers.

The American Heart Association's Council on Cardiopulmonary and Critical Care, the Scientific Committee on Tobacco and Health in the United Kingdom, and the California Environmental Protection Agency have all concluded that SHS increases the risk of heart disease [318; 319; 320].

STROKE

According to findings of the Health and Retirement Study, a national longitudinal study of U.S. adults 50 years of age and older and their spouses, never-smokers with spouses who were current smokers had a 42% increased risk of first stroke. Former smokers married to current smokers had a stroke risk similar to respondents who were current smokers [321].

LUNG DISEASE

Environmental tobacco smoke exposure is associated with respiratory symptoms, asthma, a slight impairment of lung function, and increased bronchial responsiveness [322]. A Swiss study on air pollution and lung diseases with a sample of 4,197 nonsmoking adults, showed that SHS was associated with increased risk of asthma, wheezing, bronchitis, and dyspnea [323]. Greater levels of cumulative exposure to tobacco smoke in the home and workplace are also associated with an increased risk of COPD [324]. In 2005, it was estimated that a (hypothetical) elimination of SHS in home and work environments would decrease COPD diagnoses in the United States by 18% (or 11% and 7%, respectively).

In a report by Schick and Glantz of unpublished in vivo research done by Philip Morris during the 1980s, inhaled sidestream smoke was found to be four times more toxic per gram of total particulate matter than mainstream smoke. They report that the gas/vapor phase of sidestream smoke is responsible for most of the sensory irritation and respiratory tract epithelium damage that occurs [325].

Asthma

SHS is an established trigger for the onset of asthma in children, and there is growing evidence that it is also a causal factor for asthma in adult nonsmokers [326]. Finland researchers found that subjects exposed to tobacco smoke in the workplace were twice as likely to develop asthma as those who were not exposed. Health effects for adult asthmatics include asthma attacks; increased sensitivity and reduced lung function; and irritation of the eyes, nose, and throat. Exposure to cigarette smoke for just one hour can cause 20% deterioration in short-term lung function of adults with asthma [327].

CANCER

Lung cancer holds the distinction as "the first disease linked definitively" to both active and passive smoking [299; 328; 329]. Zhong et al., based on epidemiologic studies, estimate a 30% risk of lung cancer in nonsmokers exposed to environmental tobacco smoke. Chinese women have one of the highest incidences of lung cancer in the world, yet active smoking does not appear to be a major risk factor for lung cancer in this population [328]. Smoking among Chinese women is relatively rare, and among those who do smoke, cigarette consumption is limited. However, smoking among Chinese men is especially common, so their spouses are exposed to considerable quantities of environmental tobacco smoke. Thus, nonsmoking Chinese women were an ideal population for a case-control study considering the effects of environmental tobacco smoke on lung cancer. Certain histologic types of lung cancer are more commonly associated with active smoking. The risk of developing squamous cell and small cell cancer is much higher than the risk of developing adenocarcinoma and large cell carcinoma [330]. The study by Zhong et al. showed that passive smoking also favors the development of squamous cell and small cell lung cancers over adenocarcinoma and large cell carcinoma [328].

Zhong et al. conducted a meta-analysis study on the relationship between lung cancer and environmental tobacco smoke. They found a 48% increased risk of lung cancer in nonsmoking men exposed to environmental tobacco smoke in their homes, while nonsmoking men had a 29% increased risk of lung cancer if exposed to smoke at work. A 20% increased risk of lung cancer was noted in nonsmoking women exposed to smoke in their homes, while nonsmoking women had a 15% increased risk of lung cancer if exposed to smoke at work. Furthermore, environmental tobacco smoke-exposed nonsmoking women "showed statistically significant monotonic exposure-response relationships." Finally, Zhong et al. found that childhood environmental tobacco smoke exposure did not correspond to an increased risk of lung cancer in adulthood [66].

Genetics may play an influential role in the risk of developing lung cancer from SHS exposure. Polymorphisms in the gene glutathione S-transferase (GST) M1 show a greatly increased risk of developing lung cancer with SHS exposure. GSTM1 is believed to prevent tumorigenesis by detoxifying carcinogens in tobacco smoke. Lung cancer susceptibility has been associated with anomalies in several cytochrome P450 pathways and several GST enzymes that detoxify chemical carcinogens [332; 333; 334; 335; 336]. GST enzymes are considered phase II detoxification enzymes, which conjugate glutathione to carcinogens and reactive oxygen species to detoxify them. Two of the four polymorphic gene classes of GSTs, mu (μ) and theta (θ), have been linked to tobacco-associated cancers. The GSTM1 is a variant of the mu class, which contains a null allele that may

be inactivated by a deletion of DNA coding sequences [336; 337]. Approximately 50% of the White populations of Europe and North America have homozygous null genotypes for the GSTM1 enzymatic activity [338]. Loss of GSTM1 enzymatic activity has been associated with increased risks of various cancers, including tobacco-associated lung cancer, head and neck cancer, larynx cancer, and bladder cancers. Bennett et al. found that SHS-exposed nonsmoking women with the null polymorphism represented 42% to 49% of the lung cancer cases [337]. Women with the homozygous null genotype have a greater risk of tobacco-associated cancer relative to men [339].

GSTTI is an isoenzyme of the theta class of GSTs, which is deactivated by a homozygous deletion in 11% to 18% of Whites [338]. United deficiency of GSTT1 and GSTM1 produces a dramatically increased risk for lung cancer in U.S. populations [340]. Kawajri et al. found that a mutant variation in exon 7 of the cytochrome P450 1A1 (CYP1A1) enzyme was associated with higher rates of lung cancer in the Japanese subjects studied [341]. CYP1A1 is known to activate carcinogenic polycyclic aromatic hydrocarbons including the benzo(a)pyrene component of tobacco smoking [342]. Rebbeck et al. found a synergistic increase in lung cancer risk with both homozygous deletions of GSTM1 and the valine allele variant of exon 7 in CYP1A1 [338].

Large-scale genome-wide association studies have identified several novel lung cancer susceptibility genes, including those on chromosomes 5p15.33, 15q24-25.1, and 6p21 [343]. The 5p15.33 region is associated with risks specific to adenocarcinoma of the lung. The 15q25 region contains three nicotine acetylcholine receptor subunit genes. Their polymorphisms have been associated with nicotine dependence [343]. Associations of the 6p21 region have not been consistently replicated among studies [343; 344]. Other regions (e.g., 6q23-25, 13q31.3) have also been identified by genome-wide studies as being associated with risk of lung cancer, including some studies specific to African Americans and to those who have never smoked. Further studies are necessary to assess individual susceptibility based on the combination of polymorphisms in multiple genes [343; 344; 345].

GLUCOSE INTOLERANCE/DIABETES

Houston and colleagues questioned whether active and passive smokers are more likely than nonsmokers to develop clinically-relevant glucose intolerance or diabetes. Of 4657 participants in the Coronary Artery Risk Development In Young Adults (CARDIA) study, 16.7% developed glucose intolerance at 15-year follow-up. Incidence of glucose intolerance was highest among smokers (21.8%), followed by never-smokers with passive smoke exposure (17.2%), then previous smokers (14.4%), and was lowest for never smokers with no passive smoke exposure (11.5%). The risk among current and never smokers remained after adjustment for sociodemographic, biologic, and behavioral factors, but risk in previous smokers was similar to that in never smokers without passive smoke exposure [346]. A meta-analysis conducted by Pan et al. found that both active and passive smoking are associated with significantly increased risks of type 2 diabetes. The risk was increased in individuals who had recently quit smoking, but decreased substantially as time from quitting increased. They also identified a dose-response relation for current smoking and risk of diabetes [347].

SKIN DISORDERS

Setty, Curhan, and Choi prospectively examined over a 14-year period (1991–2005) the relation between smoking status, duration, intensity, cessation, and exposure to SHS and incident psoriasis in 78,532 women from the Nurses' Health Study II. Prenatal and childhood exposure to passive smoke as well as current and past smoking and cumulative measures of smoking were associated with an increased risk of psoriasis. The risk of incident psoriasis among former smokers decreases nearly to that of never smokers 20 years after cessation [348].

WOUND REPAIR

Passive smoking is known to interfere with normal tissue repair and remodeling, though the underlying pathology is not well understood. Passive smoking has been shown to obstruct wound healing by decreasing blood flow to the damaged tissue and hindering granulation tissue formation and function. Tissue repair and remodeling is heavily reliant upon fibroblasts, which migrate to the site of damage, proliferate, and secrete cytokines, growth factors, and extracellular matrix molecules. Wong et al. found that SSW smoke causes cytoskeletal changes in fibroblasts, which may account for decreased fibroblast migration. Furthermore, excess scarring in SHS-exposed individuals is likely due to a combination of prolonged cell survival (due to a cellular stress response invoked by SHS) and the aforementioned decreased cell migration [62].

AGE-RELATED MACULAR DEGENERATION

Khan and colleagues designed a case-control study to investigate a possible relation between smoking and risk of development of age-related macular degeneration (AMD) among Whites. Although many risk factors are related to AMD (e.g., aging, hypertension, family history, obesity), they found a strong association between AMD and pack years of cigarette smoking, and the odds ratio increased with the amount smoked. Smoking impairs the functioning of the retinal pigment epithelium, causing buildup on the retina and subsequent damage to Bruch's membrane. Stopping smoking was associated with reduced odds of AMD and the risk in those who had not smoked for over 20 years was comparable to nonsmokers [349].

CERVICAL INTRAEPITHELIAL NEOPLASM (CIN)

Cervical intraepithelial neoplasm (CIN) is a precursor to cervical cancer, which is the fourth most common cause of cancer-related death in women worldwide [350]. Firmly established major risk factors for CIN include active smoking and human papillomavirus (HPV) infection. A case-control study of Taiwanese women established SHS as a major risk factor

for CIN in addition to active smoking and HPV. The authors presented an indirect and a direct potential mechanism for the development of CIN following SHS exposure. CIN could be caused indirectly by immune suppression or directly by a polycyclic aromatic hydrocarbon-DNA adduct [69]. Other studies continue to suggest an association between SHS and CIN, and while these studies continue to be conducted, few have provided conclusive results [468; 469].

NONALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease is one of the most common liver diseases in the United States. Nonalcoholic fatty liver disease covers a broad range of diseases from steatosis to nonalcoholic steatohepatitis (NASH) and can have dramatically varied underlying pathology. NASH is a significant clinical concern due to potential disease progression resulting in cirrhosis and end-stage liver disease [351]. Yuan et al. employed a mouse model transgenic for human apoB100 to consider the effect of passive smoke on cholesterol and triglyceride levels. They found no significant change in cholesterol levels with passive smoke exposure but a marked increase in triglycerides in the liver. The increased lipid accretion in hepatocytes is consistent with lipid changes seen in nonalcoholic fatty liver disease [63].

MEASURING SECONDHAND SMOKE EXPOSURE

Seventy percent to 80% of nicotine is initially metabolized to cotinine, primarily by CYP2A6 [195]. Cotinine is, for the most part, metabolized to 3'-trans-hydroxycotinine, mainly by the same CYP2A6 enzyme [352]. Both nicotine and cotinine undergo *N*-glucuronidation; however, 3'-hydroxycotinine undergoes *O*-glucuronidation [353]. Cotinine is also partly metabolized to 3'-trans-hydroxycotinine by CYP2A6 [352]. Cotinine has a half-life of 15 to 20 hours, and its serum concentrations are tenfold higher than nicotine; thus, cotinine is generally used as an index of nicotine exposure [354].

Cotinine can be measured in hair, nails, blood, saliva, or urine samples. Although other biomarkers for environmental tobacco smoke exposure exist, cotinine is currently the most sensitive and specific. Such objective quantification is especially important in studies concerning passive smoke exposure in children, as parental assessment of smoke exposure is frequently unreliable [65; 69; 277; 355; 356]. SHS exposure can also be assessed through CO breath analysis, measurement of certain carcinogens (e.g., NNAL can be found in urine, blood, and nails) or benzene, or measurement of respirable suspended particulates in the air [355].

Breath analysis has improved as an assessment tool. It utilizes the monitoring of volatile organic compounds, which are predominantly bloodborne and therefore enable monitoring of different processes in the body. One study utilizing a real-time breath analyzer identified the presence of volatile organic compounds (1,3-butadiene) after SHS exposure in the breath of nonsmokers [357]. While this method of smoking analysis is improving, studies using this tool still suffer issues of sampling and lack of normalization data. Results could be skewed by participants' varying degrees of exposure to other common sources of volatile organic compounds, for example, wood smoke and automobile exhaust [358].

Studies of genetic polymorphisms of genes that modulate cell growth and proliferation provide potentially helpful biomarkers associated with long-term exposure to carcinogens and eventual tumor formation. One such biomarker used to study lung cancer in SHS-exposed patients is the tumor suppressor gene *p53*. The *p53* gene encodes a multifactorial transcription factor that controls cellular response to DNA damage [359]. Husgafvel-Pursiainen et al. found a three- to fourfold increase in the risk of *p53* mutation in SHS-exposed patients who develop lung cancer, while in long-term heavy smokers, *p53* mutations are found in 50% of patients with lung tumors [360]. Furthermore, Husgafvel-Pursiainen et al. demonstrated that the majority of the *p53* mutations were G:C to A:T transitions. The CpG dinucleotide sites were mutational hotspots, accounting for 50% of the reported G:C to A:T substitutions within the *p53* gene. Endogenous deaminations of methylated cysteine residues or preferential carcinogen binding are proposed explanations for G:C to A:T substitutions within CpG islands. This evidence supports the role of *p53* as a biomarker for both passive and active tobacco-related carcinogenesis [360].

A combination of the measurement of body fluids for cotinine and hair for nicotine, with the questionnaire and interview-derived information, seems to be the optimal method for assessing SHS exposure. Empirical studies show general concordance of reported environmental or biologic measures of SHS exposure [361]. In addition, urinary cotinine is often used for evaluation of smoking-cessation program efficacy, monitoring of pregnancy/other at-risk groups, and assessment of occupational exposure [362].

THIRDHAND SMOKE

The term "thirdhand smoke," or "environmental tobacco smoke," has been and is often used synonymously with SHS, but it can be more accurately described as any airborne particulate matter originating from burning tobacco. It is comprised of both active mainstream smoke (tobacco smoke exhaled by active smokers) and sidestream smoke (smoke from the burning end of a cigarette) that is inhaled by nonsmokers, and evidence shows the possibility of harm for a significant period of time after the cigarette/tobacco product has been extinguished.

In a 2009 study by Winickoff et al., more than 80% of national survey respondents (regardless of smoking status) agreed that SHS was harmful to children, but only 43% of smokers and 65% of nonsmokers thought the same of thirdhand smoke (defined as "breathing air in a room today where people smoked yesterday") [363]. Thirdhand smoke, or any exposure to residual tobacco smoke contamination on surfaces or breathing air in

a room where smoking previously occurred, can be dangerous. Unfortunately, not all smokers are cognizant of these harms. Many believe that confining smoking to one room in the home or smoking in the absence of children or even smoking outside with all household windows and doors closed is enough to protect their children. Tobacco smoke does not simply disappear after cigarettes are extinguished, and it (and other toxins) may linger even with what is perceived as adequate ventilation.

Hein and colleagues were likely the first to measure nicotine content of household dust. Nicotine has a high affinity for dust particles, and the amount of tobacco smoking that occurs in the home is highly correlated with concentration of nicotine in household dust [364]. According to a study by Matt et al., vapor components of tobacco smoke "are absorbed onto walls, furniture, clothes, toys, and other objects within 10 minutes to hours after tobacco smoke has been emitted. From there, they are re-emitted into the air over the course of hours to months" [365]. Similar to findings of a study of hair nicotine levels among children in New Zealand, whether household smokers smoked indoors in the presence of their child or attempted to limit their children's smoke exposure by smoking outside or in the children's absence, the children were not protected from exposure to nicotine in the indoor air [366]. Further, skin-to-skin contact poses additional risk as nicotine was found on the index fingers of 92% of mothers in the sample [365].

Part of the reason behind the danger of thirdhand smoke may be the lead content of tobacco smoke. According to the Environmental Protection Agency, the tobacco leaves used to make cigarettes contain radioactive lead-210. Indeed, increased blood lead levels among youth is directly associated with household smoking and house dust [367]. Mainstream smoke contains at least 58 percutaneous penetration enhancers, which are used to enhance transdermal delivery of drugs. Of these, 69% are hydrophobic or strongly hydrophobic and can therefore readily permeate the skin and likely settle in percutaneous fat for continued exposure long after the cigarette has been extinguished [368]. Further, unpublished research from Philip Morris Co. shows that 4-(methylnitrosamino)-I-(3-pyridyl)-1-butanone (NNK) forms in sidestream smoke and increases up to 200% per hour during the first six hours after cigarettes are extinguished [369]. NNK has been shown to cause an exaggerated response in microglia (causing them to attack healthy brain cells) and overall neuroinflammation, which can lead to disorders such as multiple sclerosis [370].

Oie and colleagues report that low ventilation in homes can strengthen the effects of indoor pollutants. They found that odds of bronchial obstruction among children was higher in homes where they were exposed to environmental tobacco smoke as well as dampness, textile wallpaper, and plasticizer-containing surfaces [371].

The problem is not confined to homes. In a study by Matt and colleagues, it was found that cars of people who smoked in their vehicles contained elevated levels of nicotine in dust on surfaces and in the air when compared with cars of nonsmokers [372].

Haussmann et al. performed a study of fresh versus room-aged sidestream smoke to ascertain how the different types of smoke would affect rats. Their study revealed that the room-aged smoke had decreased concentrations of smoke components such as nicotine and total particulate matter. However, levels of CO remained equal to that of the fresh smoke. The rats manifested reserve cell hyperplasia in the nose and hyperplastic and metaplastic epithelial changes in the larynx; these effects were not as profound in those exposed to the room-aged smoke [373]. Rao and colleagues found that lung tissue from mice exposed to aged and diluted sidestream smoke exhibits increased angiogenesis associated with leukocyte rolling and adhesion. This phenomenon may lead to recruitment of inflammatory cells as observed in bronchitis or asthma [374]. These research studies confirm the unpublished research of Philip Morris Co. in the early 1990s, which revealed that aged sidestream smoke is more toxic to lab animals than fresh sidestream smoke [375].

INTERVENTIONS FOR SMOKING CESSATION

PRIMARY CARE INTERVENTION

Smoking cessation may be helpful in reducing firsthand and secondhand tobacco smoke exposure by eliminating the source: the smoker(s). Parents and caregivers of young children should receive cessation counseling and/or pharmacotherapy to quit smoking and eliminate the exposure of children to SHS. Parents should also be informed of the importance of a smoke-free environment for children and that it should be instituted before pregnancy. Pregnant women must learn that smoking will likely produce lasting adverse effects on their offspring. Furthermore, smoking parents should be aware that smoking is known to cause and exacerbate asthma, chronic serous otitis, otitis media, respiratory illness, and possibly childhood cancers. A healthcare provider is required to intervene if a child is suffering from one of these disorders. Healthcare providers are responsible for advising smoking parents about the harms of passive smoke as well as how to provide a smoke-free environment for their children [249]. There are many smoking cessation resources that may be provided to patients, including several "quitlines." These hotlines provide free telephone access to a smoking cessation counselor. The National Cancer Institute's quitline is 1-877-44U-QUIT (1-877-448-7848), and both English- and Spanish-speaking assistance is available. The National Cancer Institute also hosts a cessation live chat at https://livehelp.cancer.gov. The website https://smokefree.gov also offers support, tools, and expert advice through their app, text messaging, and social media networks. Assistance for issues unique to different subgroups, such as veterans, women, adolescents, adults older than 60 years of age, and those who speak Spanish, are also available.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The U.S. Preventive Services Task Force recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and FDA-approved pharmacotherapy for cessation to nonpregnant adults who use tobacco.

(https://jamanetwork.com/journals/jama/fullarticle/2775287. Last accessed June 15, 2024.)

Level of Evidence: A (There is high certainty that the net benefit is substantial.)

Although nearly 70% of patients who smoke say they would like to quit, only 7.4% are able to do so without help [376; 377]. The advice of a physician alone can increase the smoking cessation rate to 10.2% [378]. It is important for physicians to add an inquiry about smoking to the questions routinely asked while a patient's vital signs are being taken (***Figure 2***). Further assessment using an abbreviated form of the Fagerström Test for Nicotine Dependence can provide information about whether a patient is addicted to or physically dependent on nicotine. The Fagerström test is a question and answer test that rates an individual's nicotine dependence on a scale of 0 to 10 [379].

After the diagnosis of nicotine dependence is made, the next step is to assess the patient's readiness to change. The five-stage model for readiness to change can be applied to addictive behaviors such as smoking. The stages are precontemplation, contemplation, preparation, action, and maintenance. In the precontemplation stage, a patient does not believe that smoking is a problem or refuses to consider smoking cessation. In the contemplation stage, the patient recognizes that smoking is a problem and is thinking about quitting. During the preparation stage, the patient makes specific plans to stop smoking, such as setting a quit date and determining how smoking cessation will be accomplished. In the action stage, the patient stops smoking. Finally, the maintenance stage is marked by the patient's continued abstinence from smoking. Relapse to smoking behavior is common. Patients often cycle through the stages of change several times before reaching stable abstinence [380].

Interventions can be classified into behavioral, pharmacologic, and alternative methods. Behavioral interventions include physician advice and individual, group, and telephone- or Internet-based counseling. Pharmacologic interventions include NRT, sustained-release bupropion, and varenicline. Alternative interventions include hypnosis, acupuncture, exercise, lobeline, anxiolytics, mecamylamine, and opioid agonists [381].

BRIEF INTERVENTION

Brief intervention training allows healthcare professionals to offer basic support, ensuring that all smokers who come into contact with these health professionals are able to receive help as appropriate. Brief intervention offers short-term professional input, self-help leaflets and videos, and complementary therapies. This type of information can be applicable for smokers at any level. Milch et al. compared the effects of two brief interventions against treatment as usual. The minimal intervention consisted of a smoking status vital sign stamp, which documents the patient's smoking status. The enhanced intervention consisted of a five-question form that assessed the patient's level of cessation readiness and provided cessation counseling prompts for clinicians. Medical record documentation of screening for smoking and cessation advice and self-reported patient smoking cessation rates were collected 8 to 10 months after implementation. Self-reported patient smoking cessation was higher in the enhanced intervention group (12%) compared with the minimal intervention (2%) and control (4%) groups. This demonstrated that even a short questionnaire that assessed readiness to quit and provided documentation of cessation advice improved rates of clinician cessation advice and patient smoking cessation compared with no intervention [382]. In a study by Smith and Burgess of patients admitted to the hospital with diagnoses of coronary artery disease, a minimal intervention (i.e., advice from physicians and nurses and two pamphlets) resulted in 35% of the group confirmed abstinent at 12 months [383].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the U.S. Department of Health and Human Services, brief tobacco dependence treatment is effective. Individual, group, and telephone counseling are effective, and their effectiveness increases with treatment intensity. Two components of counseling are especially effective, and clinicians should use these when counseling patients making a quit attempt: practical counseling (problem-solving/skills training) and social support delivered as part of treatment.

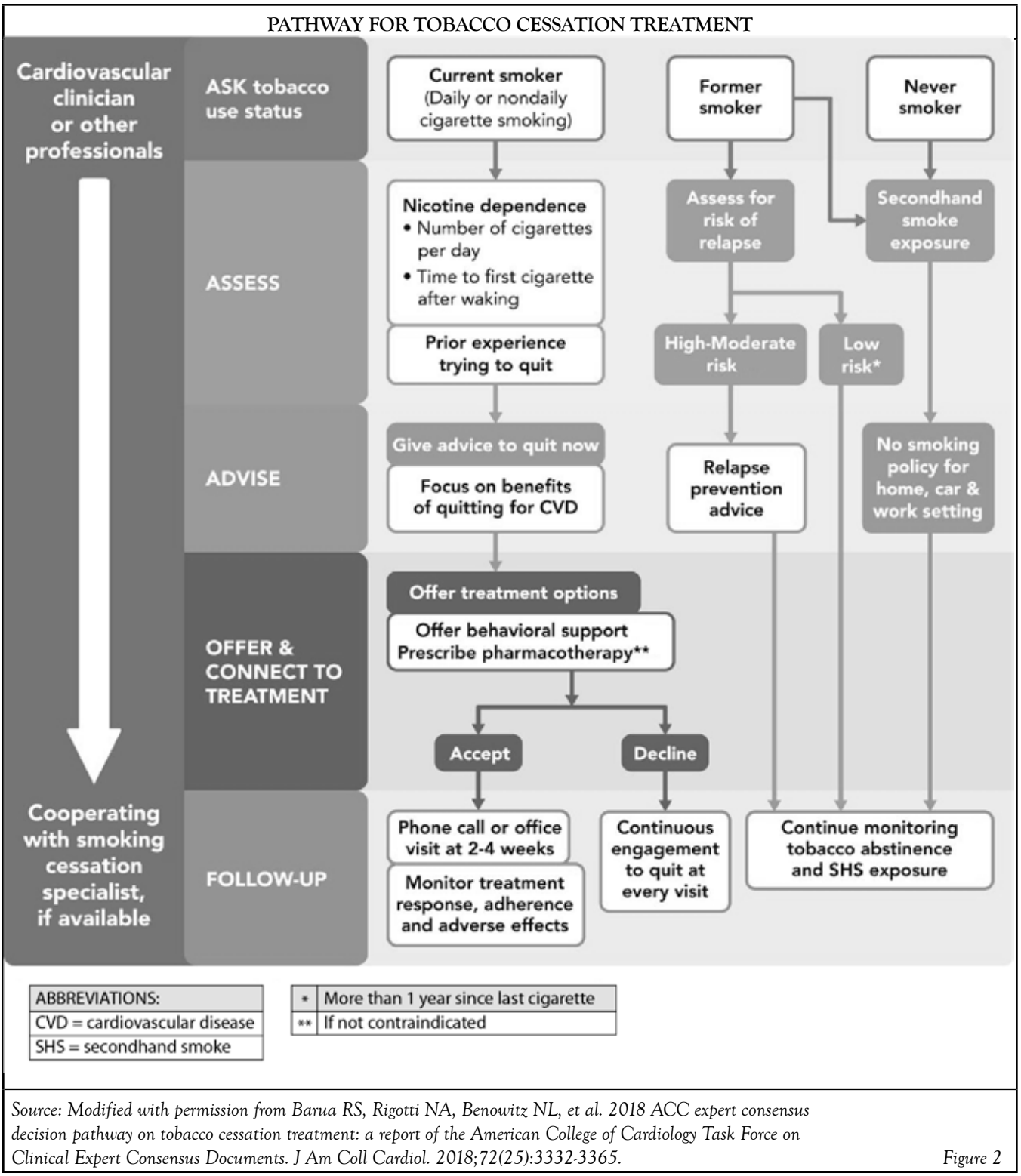
(https://www.ncbi.nlm.nih.gov/books/NBK63952. Last accessed June 15, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

5 A's

The U.S. Public Health Service Clinical Practice Guideline was updated in 2018, but continues to recommend the 5 A's approach for intervening with the patient who smokes [384; 470]:

- Ask about smoking status
- Advise to quit



Source: Modified with permission from Barua RS, Rigotti NA, Benowitz NL, et al. 2018 ACC expert consensus decision pathway on tobacco cessation treatment: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2018;72(25):3332-3365. *Figure 2*

- Assess willingness to quit
- Assist by suggesting and encouraging the use of problem-solving methods for cessation
- Arrange for follow-up contacts and relapse prevention

Mullen et al. found that simple changes in question format, such as moving away from requiring "yes" or "no" answers and allowing responses such as "I used to smoke" or "I have cut down," increased smoking disclosure by 40% [385]. Every clinician should ask patients about tobacco use and advise

them to quit. Abrupt smoking cessation with medical and psychologic assistance is more successful than tapering or "smoking less" [461].

Given the magnitude of tobacco use as a health risk, tobacco use status should be considered a vital sign requiring regular assessment [384; 386]. Nevertheless, studies continue to find that clinicians inconsistently practice assessment of tobacco use and advice to quit smoking [387]. The third step of the Five A's approach, after asking and advising, is to assess the patient's willingness to quit. For the patient who is unwilling to quit at this time, the clinician should help increase motivation by discussing the immediate and long-term risks of continued smoking, benefits of quitting, and the patient's perceived barriers to quitting. The clinician should try to make the discussion personally relevant to the patient and include risks and benefits in addition to those related to health [384]. For the patient willing to quit, the clinician should provide assistance, such as helping the patient choose a target quit date in the near future, suggesting appropriate pharmacotherapy, providing social support, advising the patient about the nature and time course of nicotine withdrawal, recommending behavioral and cognitive coping responses to use when the patient experiences urges to smoke, and perhaps making a referral to an intensive behavioral counseling program [384]. The last of the Five A's involves arranging follow-up contact. This strategy is also based on evidence that total contact time predicts treatment outcome [384]. Follow-up contact can take the form of additional office visits, telephone calls, text messages, or even written materials sent through the mail [462]. Such contact communicates the importance of the cessation attempt, provides social support, and offers the opportunity to intercede if problems have developed. Because the risk of relapse is greatest immediately after quitting, follow-up contact ideally should begin close to the target quit date [388].

MOTIVATIONAL INTERVIEWING

Introduced by Miller in 1983, motivational interviewing is a method of counseling designed to enhance patients' motivation to change by helping them explore and resolve their ambivalence about making the change [389]. It is a collaborative, non-confrontational, "guiding" approach. Motivational interviewing for tobacco cessation utilizes active listening to understand how the patient feels about his or her tobacco use in an effort to uncover any ambivalence [384]. The healthcare provider elicits the patient's own views regarding consequences of continuing to use tobacco and benefits of quitting and asks permission to share additional information on risks when necessary. Goals are developed collaboratively, based on the patient's current readiness to change. Originally developed as an intervention for alcohol abuse, it has shown promise as a successful strategy for smoking cessation. Lai et al. reviewed 28 studies and found that motivational interviewing yields a significant increase in quit rate, especially when conducted by primary care physicians or counselors for sessions lasting more than 20 minutes [390; 391]. Further, in a randomized, controlled trial, Ruger and colleagues reported that motivational interviewing for smoking cessation actually saves money, and prevents relapse, among low-income pregnant women with $628/quality-adjusted life-year saved versus usual care [392].

INTERVENTIONS FOR NON-ENGLISH-PROFICIENT INDIVIDUALS

Because communication with patients regarding cessation of smoking is a vital aspect of patient care, it is important that discussions and printed materials are provided in the language with which the individual is most comfortable. 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 patients and practitioners.

Interpreters are more than passive agents who translate and transmit information back and forth from party to party [393]. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. When providing care for patients for whom English is a second language, the consideration of the use of an interpreter and/or patient education materials in their native language may improve patient understanding and outcomes. The American Heart Association, the American Medical Association, and the American Academy of Family Physicians produce patient education references in several languages. Primary care providers may utilize these in their interactions with patients for whom English is a second language.

TREATING NICOTINE DEPENDENCE

Behavioral Modifications

Behavioral interventions are nonpharmacologic treatments delivered directly to individual smokers [388]. The main disadvantage of this approach is that relatively few smokers (about 5%) are interested in attending specific classes at any given time [394; 395]. Therefore, group sessions appear to be the most cost-effective approach to delivering smoking cessation interventions [396]. Although relatively few patients want to go to classes, physicians should still have a list of referral smoking cessation clinics in their area for those smokers who express an interest in attending them and for those who have failed to respond to other approaches. Simple text, app, and web-tailored cessation messages may also be an effective alternative for behavioral support, doubling the cessation rates. This concept has been incorporated into patient support programs provided by several manufacturers of smoking cessation products [394].

There are several behavioral interventions that have empirical support, such as multicomponent coping skills training (e.g., coping response therapy, problem-focused treatment, relapse prevention training, and cognitive-behavioral therapy). This training includes social support and didactic information about nicotine dependence, withdrawal symptoms, and situa-

tions that are risks for relapse (e.g., alcohol use, negative moods, or presence of other smokers) as well as training in the use of cognitive and behavioral responses to cope with urges to smoke that reduce the risk of relapse [397; 398]. Aversive therapy for smoking cessation, known as rapid smoking, involves smokers in a controlled clinical setting who deeply inhale on cigarettes at six-second intervals. Up to nine cigarettes would be smoked per treatment session to produce strong aversive reactions to cigarettes [399]. Aversive cigarette use greatly declined after the introduction of NRTs, and reviews have concluded that there is insufficient evidence to determine the efficacy of this method for smoking cessation [400; 401]. Another behavioral treatment, scheduled reduced smoking, involves three weeks of gradually reduced nicotine intake. In contrast with other smoking cessation strategies involving reduction of smoking, the patient does not control when and where smoking will occur. Rather, an algorithm is used to determine when each cigarette is to be smoked based on the passage of time [402].

Pharmacotherapy

The first-line pharmacologic interventions for smoking cessation are NRT, bupropion, and varenicline [381; 403]. However, no pharmacotherapy has been approved for use among pregnant or nursing women. The five forms of NRT available are the patch, gum, lozenge, nasal spray, and inhaler. A Cochrane review found that all commercially available forms of NRT increased the quit rate by 50% to 70%, independent of the intensity of additional support provided to the individual. Although support is beneficial, it does not appear to be essential to the success of NRT [404].

All available pharmacotherapies are safe for non-pregnant or nursing adults. In a 2016 analysis, varenicline outcomes are found to be equal to NRT plus counseling, and varenicline is also associated with a reduced risk of relapse [463]. Bupropion has the added advantage of reducing smoking cessation-related hyperphagia and weight gain. It is also an antidepressant and can ameliorate withdrawal-associated anhedonia and depression.

The nicotine transdermal system, otherwise known as the patch, releases nicotine steadily during an extended period, with blood levels rising within the first 2 to 4 hours and then remaining relatively constant between 8 and 24 hours after application, depending on the product used [405]. A number of transdermal nicotine-replacement systems are available over the counter. Prescribing information inserts for all transdermal nicotine products indicate that they should be used as part of a cessation program; yet, many patients receive the patch without any physician advice or behavioral support [406]. Adverse reactions to transdermal nicotine-replacement systems seldom cause discontinuation of therapy. Thirty percent to 50% of patients experience mild skin irritation with the patch. In most patients, rotating patch application sites can alleviate this problem. Sleep disruption is usually resolved by removing the patch at bedtime [407]. Unfortunately, use of the patch without any behavioral support is not likely to be successful.

The U.S. Food and Drug Administration adopted labeling for the patch, allowing use beyond the standard duration of eight weeks. This decision was based in part on data showing that extended-duration (24-week) transdermal nicotine therapy reduced the risk for smoking lapses and increased the likelihood of recovery to abstinence compared to the standard 8-week duration of therapy [408; 409].

Nicotine chewing gum is a type of NRT that may aid in smoking cessation and/or quitting smokeless tobacco. Chewing allows nicotine to be delivered quickly into the bloodstream. Typically available in either 2- or 4-mg doses, nicotine chewing gum is expected to last one to two hours. Release of nicotine from the gum is proportional to the rate of chewing, a feature that allows for self-titration [410]. However, like the patch, nicotine gum is most successful as an adjunct to behavioral interventions. Indeed, Schneider et al. showed that merely dispensing nicotine gum resulted in a lower quit rate with active gum than with placebo treatment (8% nicotine gum, 13% placebo gum) [411].

The nicotine lozenge is similar to a hard candy. It slowly dissolves in the mouth (for 20 minutes or so) to release nicotine to the brain more quickly than the patch. Shiffman, Di Marino, and Pilliteri analyzed two trials of a 21-mg nicotine patch and 4-mg lozenge to assess the efficacy of each in heavy and dependent smokers. Both therapies were found to significantly increase six-month, continuous abstinence in heavy smokers (≥40 cigarettes per day) and the highly dependent (Fagerström score >7) [412].

A 2-mg sublingual nicotine tablet has shown efficacy in several studies and has been approved in Europe to manage nicotine withdrawal [413; 414; 415]. Interestingly, one study found that being married was strongly associated with smoking cessation while on this medication [416]. Sublingual tablets (2 mg) have similar pharmacokinetics to that of the 2-mg nicotine chewing gum [417]. One study of high-dependence smokers (those who smoked their first cigarette of the day within 30 minutes of waking) found that a 4-mg nicotine lozenge significantly reduced withdrawal symptoms and cravings over six weeks of treatment [418].

Nasal nicotine spray (NNS) was approved by the FDA in 1997. Available by prescription, each spray contains 0.5 mg of nicotine, and a dose is defined as one spray in each nostril. In clinical trials, subjects were allowed to take up to 5 doses/hour, with a maximum of 40 doses/day (40 mg of nicotine). The cessation rates in trials with NNS at 1 year ranged from 15% to 25% [419; 420; 421]. A meta-analysis of nicotine replacement suggested that NNS and the inhaler might have higher quit rates than the patch or gum [422]. Indeed, nicotine administered via nasal spray is considered to be the next fastest acting delivery method after smoking and requires 11 to 13 minutes for nicotine levels to reach peak plasma concentration [423].

The FDA also approved a nicotine inhalation system consisting of a mouthpiece and a nicotine-containing cartridge. Available with a prescription, each inhaler contains 10 mg of nicotine and 1 mg of menthol, of which 4 mg of nicotine can be extracted and 2 mg are systemically available. Shallow or deep puffing results in similar nicotine absorption. Nicotine is delivered mainly to the oral cavity, throat, and upper respiratory tract, with a minor fraction reaching the lungs. A single inhaler can be used for one 20-minute period of continuous puffing or periodic use of as many as 400 puffs per inhaler. With controlled puffing in laboratory testing, venous plasma nicotine concentrations from a single inhaler puffed 80 times for 20 minutes, averaged 8.1 mcg/L at 30 minutes. Lower concentrations of 6.4 to 6.9 mcg/L have been reported for self-administration under clinical conditions. The time to reach peak plasma concentrations varies but is always significantly longer than with cigarette delivery [424].

Quitting smoking can be a difficult process, even with use of NRT. When subjects were given denicotinized cigarettes along with IV saline or nicotine, the variable most responsible for craving satisfaction, psychologic reward, and craving reduction was the denicotinized cigarette [425]. When *ad libitum* smoking of preferred brands was also allowed, the combination of nicotine-less cigarette and bolus IV nicotine were the most effective in lowering craving, negative affect, and total amount smoked [89]. Sensations in the tongue, nose, back of mouth, throat, windpipe, and chest showed strong correlation between nicotine-less cigarettes and the usual brand smoked by the subjects, perhaps explaining the strong effects on smoking suppression observed [425]. Therefore, it is important to recognize that while NRT is a key part of cessation therapy, it does not address all aspects of smoking behavior. In addition, certain smoking cessation strategies, such as NRT, have been found to be less effective among women than men. Given that researchers have found that women are 31% less likely to quit smoking successfully, further studies on gender-specific smoking cessation strategies are warranted [471].

Bupropion is an atypical antidepressant that has both dopaminergic and adrenergic actions [426]. In 1998, the slow-release preparation of bupropion became available as a prescription item specifically for smoking cessation, with the trade name Zyban. This treatment could be appropriate for smokers who do not wish to use an NRT or for those whose treatment with NRT has failed. Unlike NRT, smokers begin bupropion treatment one week prior to cessation. The suggested dosage is 300 mg/day, and the duration of treatment is 7 to 12 weeks [427]. A double-blind, placebo-controlled trial randomized patients to placebo or sustained-released bupropion (50 mg twice a day, 150 mg once a day, or 150 mg twice a day) and treated them for six weeks. Smokers with active depression were excluded, though smokers with a history of depression were not. The cessation rates at the end of therapy were 10.5%, 13.7%, 18.3%, and 24.4%, respectively. Follow-up at one year suggested a continued benefit of bupropion therapy [428]. Data from a study of bupropion combined with transdermal nicotine showed high long-term quit rates with the combination therapy [429]. Discontinuation of treatment may be appropriate for individuals unable to achieve significant progress after seven weeks, as success after this point is unlikely [430].

Another effective non-nicotine therapy for smoking cessation is varenicline tartrate, a partial agonist selective for nicotine acetylcholine receptor subtypes. Released in 2006, varenicline is available in monthly dose packs (0.5 mg and 1 mg tablets) and is approved for a 12-week course of treatment [403]. Patients able to quit smoking may continue the therapy for an additional 12 weeks for increased likelihood of long-term cessation and even up to a year in certain cases, to prevent relapse; however, medication should be stopped and patients should be reassessed if the intervention has not led to smoking cessation within the initial 12 week timeframe [430; 431; 465]. Clinical trials reveal that varenicline may be favorable to bupropion for abstinence (44% versus 30%); the medication has also been shown to help at least 20% of patients remain smoke-free for up to one year [432; 433]. Recognizing that cessation success rates increase when pharmacologic and behavioral therapies are combined, the manufacturer urges patients to combine use of varenicline with a behavioral support plan. Co-administration of varenicline and transdermal nicotine may exacerbate incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue. One study found varenicline alone to be more effective than other treatment options, while a meta-analysis study found that combination therapy (varenicline and NRT) was more effective than varenicline alone [434; 435]. In 2021, the manufacturer of Chantix, a brand of varenicline, halted production of varenicline due to unacceptably high levels of nitrosamines [480]. In addition, all lots of 0.5-mg and 1-mg tablets of Chantix were subject to a voluntary recall. However, the FDA does not recommend that patients halt use of varenicline, and generic formulations and other brands remained available.

The two second-line drugs for smoking cessation are clonidine and nortriptyline [381]. Clonidine is an antihypertensive medication that is administered orally or transdermally. It appears to increase the smoking cessation rate by approximately 11%; however, clonidine is known to produce such side effects as dry mouth, dizziness, sedation, and orthostatic hypotension [430; 436]. Clonidine has not been approved by the FDA for smoking cessation but has been used with individuals who have failed NRT or bupropion [430]. Nortriptyline is a tricyclic antidepressant that has been used to assist smoking cessation, although this is an unlabeled use [430]. A 12% improvement in cessation over controls has been reported, but the limited number of trials, combined with the adverse side effects (e.g., dry mouth, weight gain, constipation, drowsiness, sexual problems), makes nortriptyline a second-line intervention [381]. Several controlled trials have failed to show any benefit for either agent [430].

Other drugs have also been used in smoking cessation. Silver acetate, which causes cigarettes to have a bad taste, has been used as a smoking cessation aid for many years. But, there appears to be little evidence for a specific effect of silver acetate in promoting quitting [437; 438]. The addition of mecamylamine, a ganglionic blocker classified as an antihypertensive agent, to transdermal nicotine replacement has been shown to improve the abstinence rate in smokers compared with use of the patch alone [439; 440].

Additional pharmacotherapy options are in the development phase. A nicotine vaccine and other partial agonists for the nicotine receptors are being evaluated [441]. Interference with the liver enzymes that metabolize nicotine is another approach being tested [442].

In addition, it was found that methoxsalen, a compound used to treat skin disorders, reduces the activity of CYP2A6, the enzyme that metabolizes nicotine. This allows for more nicotine, whether from a cigarette or nicotine replacement, to be present in the blood and to remain there longer, which should minimize smokers' craving to smoke. However, methoxsalen has not been proven safe for use in humans and must undergo more trials before it can be used in a smoking cessation program [443]. Tranylcypromine (a monoamine oxidase inhibitor used to treat depression) and tryptamine (substrate of MAO) are also being investigated for this purpose [444].

Transcranial Magnetic Stimulation (TMS)

The FDA has cleared a transcranial magnetic stimulation (Deep TMS) system with H4-coil for use as an aid in short-term smoking cessation in adults [482]. The outpatient procedure provides noninvasive magnetic stimulation to areas of the brain known to be associated with addiction. Approval for use as a smoking cessation therapy was based on data from a multicenter, double-blind, sham-controlled trial that evaluated the efficacy and safety of the TMS system in 262 adults. Patients included in the study had a long history of smoking (average more than 26 years) and multiple failed attempts at quitting. Patients were randomized to receive either H4 deep TMS coil or sham therapy five days per week for three weeks, followed by an additional three sessions once per week for three weeks. The primary end point was the four-week continuous quit rate at any point from the start of treatment and the follow-up visit four months thereafter.

Findings showed a continuous quit rate of 17.1% in the active TMS group, compared with 7.9% in the placebo group. Among patients with four weeks of treatment, diary records, and confirmatory urine samples, the continuous quit rate was 28.4% in the TMS group and 11.7% in the placebo group. Additionally, the number of cigarettes smoked per day (secondary end point) was statistically significantly lower in the active deep TMS arm compared with placebo. TMS has been successfully used in alcohol, tobacco, cannabis, and other substance use disorders [483; 484].

Withdrawal

Similar to all addictions, nicotine withdrawal elicits a number of clinical consequences. Desire to avoid withdrawal symptoms promotes smoking. Nicotine withdrawal may last for several weeks and include such symptoms as irritability, anxiety, depression, difficulty concentrating, weight gain, restlessness, and impatience [445]. Withdrawal effects can be elicited and observed in those exposed to secondhand smoke as well as in smokers. Intensity of these withdrawal symptoms may be related to the level of nicotine dependence. In 2020, there were an estimated 30.8 million adults that smoked cigarettes [456]. Although the prevalence of cigarette smoking continues to decline, there is some evidence that this decline is a reflection of a migration to non-cigarette products, especially e-cigarettes [446; 456]

REDUCING TOBACCO SMOKE EXPOSURE

A dramatic increase in public awareness concerning the dangers of SHS has corresponded to social demand for smoking restrictions. Beginning in the 1990s, McMillen et al. found broad public support in the United States for smoking restrictions in many public places, including child care centers, hospitals, shopping malls, convenience stores, fast-food restaurants, and indoor sporting events [6]. An Irish study by Mulcahy et al. demonstrated dramatic reductions in SHS exposure following a national workplace smoking ban in Ireland. Thus, this study justified such bans given the known adverse effects of SHS, which include lung disease, heart disease, and asthma [356].

Workers suffering the detrimental effects of secondhand tobacco smoke have taken legal actions. For example, a group of 60,000 flight attendants filed a suit alleging that they had endured smoking-related illnesses from being exposed to high concentrations of environmental smoke in airplane cabins when smoking was still allowed on board [447]. Although the tobacco industry (Philip Morris, R.J. Reynolds, Brown and Williamson, the Ligett Group, and the Lorillard Group) made no admission of guilt, it established the Flight Attendant Medical Research Institute (FAMRI), a $300 million not-for-profit research institute, as a part of the settlement for flight attendants who suffered and died due to SHS exposure in air cabins. FAMRI's mission is "to sponsor scientific and medical research for the early detection and cure of diseases and medical conditions caused from exposure to tobacco smoke" [448].

Efforts to regulate tobacco products include the World Health Organization's Framework Convention on Tobacco Control (FCTC). Additionally, legislation has been passed to give the FDA regulatory authority over tobacco. The main reason for these proposals is to minimize death and disease caused by tobacco smoke by reducing the prevalence of its use and the toxicity of its products. Based on scientific studies and tobacco industry documents, it is believed that tobacco products could be made less toxic if their design, content, emissions, and manufacturing were better controlled [449].

Nationwide polls reveal broad bipartisan public support for increased taxing of tobacco [450]. State cigarette taxes have been signed into law by 53 Republican and 70 Democratic governors [451]. Since 2002, the average state cigarette tax has increased from 43.4 cents to $1.91 per pack [451; 473]. In February 2009, President Obama signed a 61.66-cent federal cigarette tax increase into law, bringing the federal cigarette tax to $1.01. As of 2021, the reported average national retail price per pack of cigarettes is $8.00 [453]. Increasing the cost of tobacco not only decreases tobacco use by creating a larger economic barrier to smoking, it also motivates people to try to quit. There is a consensus that for every 10% increase in the cost per pack of cigarettes, there is a resulting 2% decrease in adult smoking, a 3.5% decrease in young adult smoking, and a 6% to 7% decrease in childhood smoking [451].

Effective behavioral and pharmacologic treatments exist and can work if they are affordable, widely available, and used properly in clinics and communities. Smoking cessation group programs have been found to be more effective than minimal treatment programs, although less intensive treatment approaches, when combined with high participation rates, can still influence larger groups. Tobacco policies have reduced cigarette consumption at work and worksite tobacco smoke exposure [454]. Innovative partnerships with public- and population-based organizations to reach smokers and reduce exposure to tobacco have been initiated. There is a high level of support for smoking restrictions in public places to protect nonsmokers from tobacco smoke [455; 473]. Due to the 2009 federal tax increase, several health benefits and cost savings were projected, including an increase in the number of children alive today who will not become smokers (1.2 million) and $51.9 billion in long-term healthcare savings from fewer adult and youth smokers over the lifetimes of the adults who quit and kids who never start [451; 473].

Though the state and local governments and employers provide protection from tobacco smoke at work, private homes are not subject to such regulation. Educational strategies are needed to increase awareness of personal and childhood tobacco exposure both in and out of the home. As with the business microenvironment, air quality cannot be maintained if smoking is allowed indoors, even with additional ventilation and air-cleaning devices.

CONCLUSION

The purpose of this course was to increase awareness of the various implications of tobacco use and exposure and to provide examples of healthcare assessment and treatment. It should be noted that the health complications incorporated here are only part of an exhaustive list of issues linked to tobacco smoke—more findings are uncovered each day. Changes in policy (e.g., taxation, bans in federal and other public establishments, regulation by the FDA) may spur the public to take a second look before using tobacco products or exposing themselves and friends/family to its smoke. However, it is important to continue to combat tobacco use and exposure at the primary care level at every possible opportunity. Brief intervention methods are more helpful than many realize. Further, although cigarettes have historically been implicated for the majority of health problems, it is important to be cognizant of other tobacco products' health effects and the evolving trends of tobacco use.

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COURSE TEST - #91784 SMOKING AND SECONDHAND SMOKE

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 May 31, 2025.

1. **Tobacco was originally marketed in Europe for many ailments, including**
   A) *insomnia.*
   B) *dental pain.*
   C) *rheumatism.*
   D) *acute appendicitis.*

2. **Early warnings of tobacco's detrimental effects can be traced to the publication of *A Counterblaste to Tobacco*, which was published by**
   A) *John Rolfe.*
   B) *Jean Nicot.*
   C) *King James I.*
   D) *Christopher Columbus.*

3. **Which of the following statements about smoking prevalence is TRUE?**
   A) *Current use of any tobacco product is highest among Hispanics.*
   B) *Approximately 1.6 million Americans initiated cigarette smoking in 2019.*
   C) *More than 20% of the U.S. population 18 years of age or older are current smokers.*
   D) *Higher levels of education are correlated with an increased likelihood of having smoked cigarettes in the past month.*

4. **All of the following are TRUE about bidis, EXCEPT:**
   A) *Bidis are filled with sun-dried tobacco.*
   B) *Bidis can be vanilla or cherry flavored.*
   C) *Bidis contain more ammonia than a regular cigarette.*
   D) *Bidis are rolled into air-cured and fermented tobacco wrappers.*

5. **Kreteks, or clove cigarettes, are composed of approximately what percentage of tobacco?**
   A) *5% to 15%*
   B) *20% to 40%*
   C) *40% to 60%*
   D) *60% to 80%*

6. **Mainstream smoke is**
   A) *smoke inhaled by the smoker.*
   B) *smoke exhaled by the smoker.*
   C) *the main component of secondhand smoke.*
   D) *smoke emitted by the burning end of a cigarette.*

7. **Though it varies between smokers, the breathing pattern of a smoker is different from normal tidal breathing because it is**
   A) *deeper and slower.*
   B) *shallower and slower.*
   C) *deeper and more rapid.*
   D) *shallower and more rapid.*

8. **After the commencement of smoking, nicotine from cigarette smoke reaches peak plasma concentrations in**
   A) *20 to 30 seconds.*
   B) *1.5 to 3 minutes.*
   C) *20 to 30 minutes.*
   D) *one to three hours.*

9. **Which of the following is NOT a risk factor for the development of a smoking habit?**
   A) *Affiliation with smoking peers*
   B) *Comorbid psychiatric disorders*
   C) *Disinterest in body image in girls*
   D) *Presence of a smoker in the household*

10. **Cigarette smoke affects many organ systems, but the one with the most clinical importance in developing dependence is the**
    A) *skeletal system.*
    B) *circulatory system.*
    C) *respiratory system.*
    D) *central nervous system.*

11. **Studies have shown that nicotine from cigarette smoke reduces global cerebral blood flow most markedly in the**
    A) *insula.*
    B) *cerebellum.*
    C) *occipital cortex.*
    D) *right hemisphere.*

12. Neurons located in the ventral tegmental area become more active with nicotine administration, leading to
- A) *an increase of hunger.*
- B) *a stimulation of dysphoria.*
- C) *an increase in dopamine release.*
- D) *a reduction in self-administered nicotine.*

13. Which of the following statements about the psychologic effects of smoking is TRUE?
- A) *Smoking decreases stress.*
- B) *Smoking increases concentration.*
- C) *Smoking gives a true sense of pleasure and release.*
- D) *Smoking causes a decline in cognitive functioning.*

14. What percentage of smokers develop COPD?
- A) *Less than 5%*
- B) *15% to 20%*
- C) *20% to 30%*
- D) *More than 35%*

15. Cigarette smoking
- A) *decreases thrombosis.*
- B) *decreases inflammation.*
- C) *impacts endothelial function.*
- D) *decreases oxidation of low-density lipoprotein cholesterol.*

16. What percentage of persons with alcohol use disorder also smoke cigarettes?
- A) *25% to 40%*
- B) *40% to 65%*
- C) *65% to 80%*
- D) *80% to 95%*

17. Smoking is highly comorbid with
- A) *schizophrenia.*
- B) *panic disorder.*
- C) *major depression.*
- D) *All of the above*

18. Fetal nicotine exposure
- A) *elicits only a short-term alteration in brain cells.*
- B) *stimulates an increase in arousal responsiveness to hypoxia.*
- C) *has no adverse effect on eventual programming of synaptic competence.*
- D) *results in permanent abnormalities of the dopaminergic regulation of the brain.*

19. On average, fetuses of mothers who smoke
- A) *have altered cardiac cell differentiation.*
- B) *are less likely to develop ventricular arrhythmias.*
- C) *have an increased number of cardiac β-adrenergic receptors.*
- D) *manifest a decrease in cardiac volume growth between 23 and 27 weeks' gestation.*

20. Which of the following statements about the effects of pediatric exposure to SHS is TRUE?
- A) *Nicotine exposure elicits an increase in physical fitness.*
- B) *Young children have lower ventilation rates and therefore lower levels of SHS exposure.*
- C) *Parental smoking is negatively correlated to their offspring's smoking as adolescents and adults.*
- D) *SHS exposure during childhood is potentially more dangerous to neurodevelopment than in utero exposure.*

21. Active and passive smoking are known to
- A) *decrease incidences of thrombosis.*
- B) *decrease occurrences of atherosclerosis.*
- C) *increase incidences of cardiac arrhythmias.*
- D) *promote the oxygen-carrying capacity of blood.*

22. Adult exposure to SHS is associated with
- A) *asthma.*
- B) *decreased bronchial responsiveness.*
- C) *a dramatic impairment of lung function.*
- D) *All of the above*

23. Cotinine can be found in all of the following, EXCEPT:
- A) *Hair*
- B) *Urine*
- C) *Blood*
- D) *Breath*

24. The most sensitive biomarker used to confirm the extent of SHS exposure to nonsmokers is
- A) *cotinine.*
- B) *nicotine.*
- C) *benzine.*
- D) *albumin.*

25. "Thirdhand" smoke is
- A) *tobacco smoke contamination of dust.*
- B) *air in a room where smoking previously occurred.*
- C) *residual tobacco smoke contamination on surfaces.*
- D) *All of the above*

Test questions continue on next page ➞

26. Brief interventions offer
- A) *self-help leaflets or videos.*
- B) *extensive professional input.*
- C) *nicotine-replacement therapy.*
- D) *sustained-release bupropion treatment.*

27. The Clinical Practice Guideline recommends the 5 A's approach for intervening with a patient who smokes. After the practitioner establishes that a patient smokes by asking about his or her smoking status, the second of the five steps is to
- A) *advise the patient to quit.*
- B) *arrange for follow-up contacts.*
- C) *assess the patient's willingness to quit.*
- D) *assist the patient to use problem-solving methods.*

28. Nicotine-replacement therapy is available in all of the following forms, EXCEPT:
- A) *Patches*
- B) *Shots and implants*
- C) *Nasal spray and inhalers*
- D) *Gum, lozenges, and sublingual tablets*

29. The suggested dosage of bupropion for smoking cessation is
- A) *50 mg per day.*
- B) *150 mg per day.*
- C) *200 mg per day.*
- D) *300 mg per day.*

30. It is estimated that the 2009 tax increase on tobacco products will result in
- A) *no change in national smoking patterns.*
- B) *a decreased level of support for smoking restrictions.*
- C) *1.2 million children alive today never becoming smokers.*
- D) *$4 million in healthcare savings from fewer smoking-related strokes and myocardial infarctions.*

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