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# *Pain Management Pearls: Opioids and Culture*

**Includes 1 Pharmacotherapeutic/Pharmacology Hour**

***Audience***
This course is designed for nurses, physicians, and allied health professionals who may intervene to improve the treatment of pain in diverse patient populations.

***Course Objective***
The purpose of this course is to increase clinicians' knowledge and awareness of the appropriate prescription of opioids and the impact of culture on issues of pain and pain management in order to improve the provision of care and patients' quality of life.

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

1. Discuss characteristics of appropriate and inappropriate opioid prescribing and contributory factors to both.
2. Outline the appropriate periodic review and monitoring of patients prescribed opioid analgesics.
3. Describe necessary components of patient/caregiver education for prescribed opioid analgesics, including guidance on the safe use and disposal of medications.
4. Analyze how culture, race and ethnicity influence how pain is defined, expressed, and experienced.

***Faculty***
**Mark Rose, BS, MA**, is a licensed psychologist and researcher in the field of alcoholism and drug addiction based in Minnesota. He has written or contributed to the authorship of numerous papers on addiction and other medical disorders and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to various law firms on matters related to substance abuse, is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine, and is a member of several professional organizations.

**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.

Previously acting as a faculty member at Capella University and Northcentral University, Dr. Yick Flanagan is currently a contributing faculty member at Walden University, School of Social Work, and a dissertation chair at Grand Canyon University, College of Doctoral Studies, working with Industrial Organizational Psychology doctoral students. She also serves as a consultant/subject matter expert for the New York City Board of Education and publishing companies for online curriculum development, developing practice MCAT questions in the area of psychology and sociology. Her research focus is on the area of culture and mental health in ethnic minority communities.

***Faculty Disclosures***

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

Contributing faculty, Alice Yick Flanagan, PhD, MSW, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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***Division Planner Disclosure***

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## INTRODUCTION

Pain affects all domains of life, and clinicians have few effective tools at their disposal to help these patients [1]. Opioids remain the strongest group of analgesic drugs available [2]. Millions of patients are safely and effectively maintained on relatively high-dose opioids for chronic, severe pain and require these medications to function. Public pressure and the mischaracterization of patients as "drug addicts" has increasingly deterred prescribers from treating patients with chronic pain successfully managed with opioids for years or decades rather than improving safety practices [3; 4]. However, opioids, like many medications, have serious risks and should not be treated like a cure-all [5]. This dichotomy has resulted in many patients for whom opioid analgesics are appropriate increasingly experiencing barriers to pain relief.

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 African American patients is especially widespread, from prevalent misperceptions that this group has higher pain tolerance and is more likely to abuse their opioid prescription [6]. 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.

## OPIOID MANAGEMENT OF CHRONIC PAIN

### What are the ten essential steps of opioid prescribing for chronic pain that can help mitigate any potential problems?

All patients with pain have a level of risk that can only be roughly estimated initially and modified over time as more information is obtained. There are ten essential steps of opioid prescribing for chronic pain to help mitigate any potential problems [7]:

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

Despite limited evidence for reliability and accuracy, screening for opioid use is recommended by the American Society of Interventional Pain Physicians, as it will identify opioid abusers and reduce opioid abuse.

(https://painphysicianjournal.com/2012/july/2012;%2015;S67-S116.pdf. Last accessed July 27, 2020.)

**Level of Evidence**: Limited (Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality trials, important flaws in trial design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.)

### INFORMED CONSENT AND TREATMENT AGREEMENTS

The initial opioid prescription is preceded by a written informed consent or "treatment agreement" [8]. This agreement should address potential side effects, tolerance and/or physical dependence, drug interactions, motor skill impairment, limited evidence of long-term benefit, misuse, dependence, addiction, and overdose. Informed consent documents should include information regarding the risk/benefit profile for the drug(s) being prescribed. The prescribing policies should be clearly delineated, including the number/frequency of refills, early refills, and procedures for lost or stolen medications.

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

It is important to remember that treatment agreements are only one aspect of developing a safe opioid use plan. The evidence to support the use of such agreements to decrease the misuse of opioids is relatively weak, with little or no proof of improvements in adherence or patient care [9].

## INITIATING A TRIAL OF OPIOID THERAPY

Opioid therapy should be presented as a trial for a pre-defined period (e.g., ≤30 days). As noted, the goals of treatment should be reasonable improvements in pain, function, depression, anxiety, and avoidance of unnecessary or excessive medication use [8]. The treatment plan should describe therapy selection, measures of progress, and other diagnostic evaluations, consultations, referrals, and therapies.

In opioid-naïve patients, start at the lowest possible dose and titrate to effect. Dosages for opioid-tolerant patients should always be individualized and titrated by efficacy and tolerability. The need for frequent progress and benefit/risk assessments during the trial should be included in patient education. Patients should also have full knowledge of the warning signs and symptoms of respiratory depression.

Prescribers should be knowledgeable of federal and state opioid prescribing regulations. Issues of equianalgesic dosing, close patient monitoring during all dose changes, and cross-tolerance with opioid conversion should be considered. If necessary, treatment may be augmented, with preference for nonopioid and immediate-release opioids over extended-release/long-acting (ER/LA) opioid formulations. Taper opioid dose when no longer needed [10].

## PERIODIC REVIEW AND MONITORING

### What are the 5 A's of monitoring chronic opioid response?

When implementing a chronic pain treatment plan that involves the use of opioids, the patient should be frequently reassessed for changes in pain origin, health, and function [8]. This can include input from family members and/or the state prescription drug monitoring program. Prescription drug monitoring programs are one of the most effective measures for reducing opioid analgesic diversion and abuse, but their efficacy is undermined by inconsistent use [9]. During the initiation phase and during any changes to the dosage or agent used, patient contact should be increased. Decisions regarding the continuation, modification, or termination of opioid therapy for pain should be based on evaluation of the patient's progress and the absence of substantial risks or adverse events [8]. At every visit, chronic opioid response may be monitored according to the 5 A's [11]:

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

**Assessment During Ongoing Opioid Therapy**

Signs and symptoms that, if present, may suggest a problematic response to the opioid and interference with the goal of functional improvement include [11]:

- Excessive sleeping or days and nights turned around
- Diminished appetite
- Inability to concentrate or short attention span
- Mood volatility, especially irritability
- Lack of involvement with others
- Impaired functioning due to drug effects
- Use of the opioid to regress instead of re-engaging in life
- Lack of attention to hygiene and appearance
- Escalation of pain and/or pain medication dose
- Increasing number of medications prescribed to treat the side effects of opioids

Patients who display any of these signs or symptoms should be assessed for potential opioid misuse or use disorder/addiction. Persons in active addiction should be referred to an addiction and/or pain specialist.

The decision to continue, change, or terminate opioid therapy is based on progress toward treatment objectives and absence of adverse effects and risks of overdose or diversion [8]. Satisfactory therapy is indicated by improvements in pain, function, and quality of life. Brief assessment tools to assess pain and function may be useful, as may UDTs. Treatment plans may include periodic pill counts to confirm adherence and minimize diversion.

Information obtained by patient history, physical examination, and interview, from family members, a spouse, or state prescription drug monitoring database, and from the use of screening and assessment tools can help the clinician to stratify the patient according to level of risk for developing problematic opioid behavioral responses. A urine drug test should be performed prior to initiating opioid treatment.

Low-risk patients receive the standard level of monitoring, vigilance, and care. Moderate-risk patients should be considered for an additional level of monitoring and provider contact, and high-risk patients are likely to require intensive and structured monitoring and follow-up contact, additional consultation with psychiatric and addiction medicine specialists, and limited supplies of short-acting opioid formulations.

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

## PATIENT AND CAREGIVER EDUCATION

### Safe Use of Opioids

Patients and caregivers should be counseled regarding the safe use and disposal of opioids. As part of its mandatory Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioids, the 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 unless prescribed [10]. A copy of this form may be accessed online at https://www.fda.gov/media/86281/download.

When prescribing opioids, clinicians should provide patients with the following information and instructions [10]:

- 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

### Disposal of Opioids

#### What is the universal recommendation for the proper disposal of unused opioids?

There are no universal recommendations for the proper disposal of unused opioids, and patients are rarely advised of what to do with unused or expired medications. According to the Office of National Drug Control Policy, most medications that are no longer necessary or have expired should be removed from their containers, mixed with undesirable substances (e.g., cat litter, used coffee grounds), and put into an impermeable, nondescript container (e.g., disposable container with a lid or a sealed bag) before throwing in the trash [12]. The FDA recommends that most opioid 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 [12]. Disposal by flushing down the toilet provides immediate and definitive elimination of safety hazards from intentional use or accidental exposure involving opioid products. All transdermal patch opioid products should be flushed down the toilet after folding in half by adhesive side against adhesive side [13]. Patients should be advised to flush prescription drugs down the toilet only if the label or accompanying patient information specifically instructs doing so. Flushing unused medications has been the subject of controversy, with some state governments and boards recommending against the practice due to pollution concerns and effects on waterways and wildlife [14].

The American Medical Association recommends the following three steps to promote the safe storage and disposal of opioids [15]:

- Educate patients about the safe use of opioids, including not sharing prescriptions with others.
- Remind patients that medications should be stored out reach of children and in a safe place—preferably locked—to prevent other family members and visitors from taking them.
- Talk to patients about the most appropriate way to dispose of expired, unwanted, and unused medications. The preferred option is that unwanted or unused pills, liquids or other medications should be disposed of in a local "take-back" or mail-back program or medication drop box at a police station, pharmacy, or authorized collection site. Contact your state law enforcement agency or visit https://takebackday.dea.gov to determine if a program is available in your area.

### CONSULTATION AND REFERRAL

It is important to seek consultation or patient referral when input or care from a pain, psychiatry, addiction, or mental health specialist is necessary. Clinicians who prescribe opioids should become familiar with opioid addiction treatment options (including licensed opioid treatment programs for methadone and office-based opioid treatment for buprenorphine) if referral is needed [8].

Ideally, providers should be able to refer patients with active substance abuse who require pain treatment to an addiction professional or specialized program. In reality, these specialized resources are scarce or non-existent in many areas [8]. Therefore, each provider will need to decide whether the risks of continuing opioid treatment while a patient is using illicit drugs outweigh the benefits to the patient in terms of pain control and improved function [16].

### MEDICAL RECORDS

Documentation is a necessary aspect of all patient care, but it is of particular importance when opioid prescribing is involved. All clinicians should maintain accurate, complete, and up-to-date medical records, including all written or telephoned prescription orders for opioid analgesics and other controlled substances, all written instructions to the patient for medication use, and the name, telephone number, and address of the patient's pharmacy [8]. Good medical records demonstrate that a service was provided to the patient and that the service was medically necessary. Regardless of the treatment outcome, thorough medical records protect the prescriber.

### DISCONTINUING OPIOID THERAPY

The decision to continue or end opioid prescribing should be based on a joint discussion of the anticipated benefits and risks. An opioid should be discontinued with resolution of the pain condition, intolerable side effects, inadequate analgesia, lack of improvement in quality of life despite dose titration, deteriorating function, or significant aberrant medication use [8].

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

## THE IMPACT OF CULTURE ON PAIN AND PAIN MANAGEMENT

Patients' experiences of pain may be frustrating if they defy biomedical explanation, and the treatment of pain tends to be stigmatized [17]. When culture, race, and ethnicity are taken into consideration, the treatment of pain becomes even more complex. Practitioners should address how patients construct the meaning and experiences of pain rather than simply dealing with a set of medical procedures and routines [17].

Practitioners working with patients experiencing pain should be aware of the patient's cultural value and belief systems and how they impact their pain experience and also how their own cultural background and professional culture/system affects how they view pain. Furthermore, culture can influence access to and utilization of pain management services and medications and provider communication [22]. For the most part, practitioners are trained and socialized from a biomedical tradition [23]. Practitioners should reflect on their own experiences and the values and beliefs they attribute to pain [24]. Take a moment to consider the following self-reflective questions [24].

**Pain Experiences in Childhood**

- When you were a child, how did those who cared for you react when you were in pain?
- How did they expect you to behave when you had a minor injury?
- How did they encourage you to cope when you had severe pain?
- How did they encourage you to behave during an injection or procedure?
- When those who cared for you as a child were in pain, how did they react?
- What words did they use to describe the pain?
- How did they cope with their pain?
- Do you tend to follow their example?

**Pain Experiences in Adulthood**

- What painful experiences have you had as an adult (e.g., childbirth, fracture)?
- How did you express (or not express) your pain?
- Did the pain cause you fear? What were you afraid of?
- How did you cope with the pain?
- How did you want others to react while you were in pain?

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**Pain Experiences by Patients**

- Have you ever felt uncomfortable with the way a patient was reacting (or not reacting) to pain?
- What did the patient do that concerned you?
- Why did you feel that way?
- Do you make value judgments about patients in pain who:
  - Behave more stoically or expressively than you would in a similar situation?
  - Ask for pain medication frequently or not often enough?
  - Choose treatments you do not believe are effective or with which you are unfamiliar?
  - Belong to a cultural group (e.g., ethnic, linguistic, religious, socioeconomic) different from your own?
- Do you tend to feel certain reactions to, descriptions of, or treatments for pain are "right" or "wrong?" What about these reactions makes them seem right or wrong?

## FACTORS THAT CONTRIBUTE TO RACIAL AND ETHNIC DISPARITIES IN 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 [25]. Specifically, African 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 [20].

Analysis of a national dataset found that African Americans were less likely to be prescribed opioids for back pain and abdominal pain compared with non-Hispanic white Americans [26]. 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 [27]. In this study, 59.6% of the white patients received epidural analgesia, compared with 49.5% of African 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 [27].

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 [28]. In addition, African 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 [29; 30]. Recent immigrants from Japan, for example, are going to be very different from native-born Japanese who have resided in the United States for generations [29]. However, researchers have often combined these groups, as challenges in recruitment yield small sample sizes that make it difficult for statistical analyses to be meaningful. The literature has identified a variety of reasons for these disparities stemming from several factors [31].

**Barriers Related to Western Biomedical Culture**

Western biomedical culture emphasizes a clear dichotomy between the mind and the body as well as what is observable (objective) and what is not (subjective) [32]. Pain is not easily measured, making its assessment and treatment a challenge in Western medicine [32]. In addition, many healthcare professionals may not be adequately trained to incorporate spirituality in the management and treatment of pain for patients who desire to incorporate a more holistic approach [33]. The Western American medical paradigm also leans toward cure rather than care [32]. Patients who present with symptoms that lead to a diagnosis for which there is a clear pathway of interventions and treatment are "favored." Because of the subjective nature of pain, healthcare professionals must often make clinical decisions in the face of a lack of absolute, clear physical evidence [34].

**Societal and Institutional Barriers**

### What are societal/institutional barriers to effective pain management in racial and ethnic minority groups?

Societal and institutional barriers include racism, discrimination, poverty, lack of health insurance, and deleterious environmental factors in communities [35]. For example, groups that have historically (or currently) been victims of institutional racism and discrimination are more likely to delay seeking help for pain [28]. Some studies indicate that African American men may experience higher levels of pain intensity in part due to their experiences with different forms of racial discrimination [20]. Even today, racial and ethnic minority patients are more likely to be placed in a negative valenced relationship [34]. In the context of pain management, healthcare providers are more likely to discount the pain due to the negative valenced relationship triggered by racism and discrimination [34].

It has been shown that physicians tend to have less involved communication and less participatory interactions with racial minority patients and low-income patients [32]. In addition, the stereotype that certain racial minority groups come from chaotic and disorganized families and environments increases the likelihood of healthcare professionals labeling them as "difficult." Just as healthcare professionals may have preconceived notions about patients, patients may have pre-existing assumptions about the provider. For example, one study of Native American patients found that the participants tended to feel that healthcare professionals were not interested in hearing about their pain experience and did not have confidence that they would be helped [36]. Thus, a cycle of myths and stereotypes continues.

One oft-cited study found that three-quarters of pharmacies located in areas of New York City with a high proportion of racial and ethnic minority residents did not stock adequate supplies of opioid analgesics [37]. Some pharmacists attributed the low supply to lower demand, but others cited factors related to racism and discrimination. In addition, pharmacies in areas with high concentrations of racial minorities are more concerned with burglaries, additional regulations, and penalties imposed by state and federal drug-enforcement agencies than pharmacies in predominantly white neighborhoods [37].

**Healthcare Professional-Related Barriers**

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 [38]. 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 [39].

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 improves and racial and ethnic minority patients with pain fare better [40]. 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 [41; 42].

**Patient-Related Barriers**

Patient barriers to effective pain management include fear and anxiety about substance misuse and addiction, cultural values such as fatalism (i.e., pain is inevitable), and ideas about being a good patient [31]. Cultural values about pain coping, definitions, expression, and experience may also be patient-related barriers. For example, those with a fatalistic perspective of pain are often stoic. A qualitative study of Somali women found that the participants felt wailing or crying about one's pain was a sign of weakness [43]. Similarly, Hispanics and African Americans are more likely to embrace the importance of being stoic and are less likely to ask for pain medication [28]. Studies also show that Hispanic and African American patients with cancer tend to underreport their pain for fear of being labeled as complainers or of distracting the physicians treating their illness [44]. Some patients will not ask questions for fear that would be viewed as challenging an authority figure [45]. Some ethnic/racial minority patients disclose that they avoid pain medications because they overestimate the risk dependence [45; 46; 47].

## ALTERNATIVE REMEDIES

Practitioners should explore both traditional biomedical pain management interventions and non-traditional alternative remedies (as appropriate) when working with racial and ethnic minority patients. Complementary self-management approaches for pain can be generally classified as mind/body approaches or natural products [48]. Mind/body approaches include meditation, yoga, acupuncture, and breathing techniques. Natural products include herbs, vitamins, and topical ointments [48]. Some patients may be more receptive to traditional healing methods (e.g., herbal remedies, traditional healers) [36]. In focus groups, Native American participants reported using a range of alternative therapies for pain, including acupuncture, massage, chiropractic treatment, and guided imagery [39].

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Alternative remedies for pain can be classified into five different areas, and many can be used as adjuncts to conventional therapies [49; 50]:

- Alternative medications: Nonpharmacologic substances, such as those associated with homeopathic medicine, traditional Chinese medicine, and Ayurveda medicine
- Mind-body interventions: Interventions that focus on using the mind to influence bodily symptoms, including biofeedback, meditation, music therapy, and guided imagery. Mind-body interventions help reduce pain and improve other comorbid conditions, such as depression.
- Biologically based interventions: Consumption of biologic products (e.g., herbs, vitamins, foods)
- Manipulation strategies: Adjustment of focused areas of the body (e.g., chiropractic measures, massage, acupuncture)
- Energy therapies: Balancing energy fields (e.g., electromagnetic therapy, reiki, qigong)

Some cultural groups subscribe to the hot/cold theory of disease, which argues that illnesses are the result of bodily imbalances and that foods and alternative medications are inherently "hot" or "cold." Pain is considered a "cold" disease, and some patients who adhere to traditional healing will take this into account when selecting and adhering to treatment approaches [51].

## END-OF-LIFE CONSIDERATIONS

Palliative care is the noncurative care provided to terminally ill patients to relieve symptoms and improve quality of life [52]. The goal of palliative care is to not only meet patients' physical needs but also address their psychologic, social, religious/spiritual, and cultural needs [53]. Even across cultures, there appear to be common denominators for effective palliative care. In an analysis of studies on palliative care in various ethnic/racial minority groups, researchers found common cultural themes that cut across all groups in the area of palliative care [54]. These included:

- Pain management
- Support to achieve closure (i.e., resolve social and emotional concerns that are hindering well-being)
- Spiritual and religious care
- Support to family and friends
- Focus on the quality of life

One concept that has been helpful in pain management at the end of life is the idea of total pain. Total pain considers the contributions of physical noxious stimuli, affect/emotional discomfort, interpersonal conflicts, and nonacceptance of one's own dying [55]. A patient's cultural perspective can influence any of these factors and/or how they are conveyed. The most important consideration at the end of life is that the patient's wishes are followed, and this almost always includes a desire for a pain-free death, regardless of background and culture.

**Customer Information/Evaluation insert located between pages 32–33.**

# *Fibromyalgia*

**Includes 1 Pharmacotherapeutic/Pharmacology Hour**

***Audience***
This course is designed for nurses, physicians, physician assistants, and other healthcare professionals involved in the diagnosis, treatment, and care of patients with fibromyalgia.

***Course Objective***
The purpose of this course is to provide healthcare professionals with the information necessary to diagnose and treat fibromyalgia according to evidence-based or guideline-endorsed recommendations in order to improve patient quality of life.

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

1. Outline the diagnostic criteria established for fibromyalgia, and discuss potential difficulties in establishing a diagnosis.
2. Identify appropriate treatment modalities for patients with fibromyalgia and patient education and follow-up needs.

***Faculty***
**Lori L. Alexander, MTPW, ELS, MWC**, is President of Editorial Rx, Inc., which provides medical writing and editing services on a wide variety of clinical topics and in a range of media. A medical writer and editor for more than 30 years, Ms. Alexander has written for both professional and lay audiences, with a focus on continuing education materials, medical meeting coverage, and educational resources for patients. She is the Editor Emeritus of the American Medical Writers Association (AMWA) Journal, the peer-review journal representing the largest association of medical communicators in the United States. Ms. Alexander earned a Master's degree in technical and professional writing, with a concentration in medical writing, at Northeastern University, Boston. She has also earned certification as a life sciences editor and as a medical writer.

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***Faculty Disclosure***
Contributing faculty, Lori L. Alexander, MTPW, ELS, MWC, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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

***Division Planner***
Jane C. Norman, RN, MSN, CNE, PhD

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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

Fibromyalgia is a complex rheumatic disorder characterized by chronic widespread musculoskeletal pain and focal tenderness (tender points), often accompanied by fatigue, other somatic complaints, and disturbances of affect and cognition [1]. The definition of the syndrome has been expanded to include the presence of fatigue, stiffness, and nonrestorative sleep; however, individuals with fibromyalgia usually have a broad range of additional symptoms and comorbidities [1; 2; 3]. The onset of fibromyalgia is insidious, symptoms wax and wane in intensity, and the course is variable [3; 4].

Acceptance of fibromyalgia as a discrete clinical entity (not associated with an apparent organic disease) has been slow [3; 5; 6; 7; 8]. In fact, at one time, there was a 40% bias of a person with fibromyalgia being labeled "neurotic" [3]. Despite increasing support for the validity of the syndrome, consensus is lacking about its cause, diagnosis, and optimal treatment [6; 8; 9].

Fibromyalgia has a substantial negative effect on physical, psychologic, and social well-being, and the syndrome is associated with a significant burden in terms of both disability and healthcare costs. Fibromyalgia has been found to have a greater negative impact on quality of life than many other diseases, including osteoarthritis, chronic obstructive pulmonary disease, and permanent ostomies [9]. Activities of daily living and work within the home are often substantially limited. In a large survey of women 31 to 78 years of age, more than 25% had difficulty taking care of personal needs and bathing and more than 60% had difficulty doing light housework, going up/down one flight of stairs, walking one-half mile, or lifting/carrying 10 pounds [10]. The average survey respondent was assessed as having less functional ability than a typical woman in her 80s [10]. Approximately 20% to 50% of individuals with fibromyalgia are able to work few or no days; 36% are absent from work two or more days each month; 31% have lost employment; and 26% to 55% receive disability or Social Security payments [5].

The economic burden is also high. According to studies of large U.S. claims databases, the healthcare costs of fibromyalgia are two to three times higher (compared with controls) as a result of more visits to the physician's office or emergency department and a higher number of prescription medications [11; 12]. Healthcare utilization and costs are high in the year preceding as well as following the initial diagnosis of fibromyalgia [12].

## EPIDEMIOLOGY

According to prevalence and population estimates, fibromyalgia affects approximately 5 million people in the United States [13]. Determining the true prevalence is difficult because of the problems associated with defining its diagnosis according to the available criteria [5; 13]. The prevalence is estimated to be 2% to 8% of the population and increases with age [14; 15].

As with autoimmune diseases, the prevalence of fibromyalgia is higher among women than men, although data are conflicting. A female-to-male ratio of 6:1 to 9:1 has been reported in some studies [5; 12; 16]. However, estimates that use newer, symptom-based diagnostic criteria show a female-to-male ratio of 2:1 [14; 15].

The prevalence of fibromyalgia is 5% to 6% among patients seen in family or general medicine practice settings and among 15% to 20% of patients seen by rheumatologists [8]. As such, the syndrome is among the 100 most common diagnoses made in the family medicine setting, as well as one of the most common diagnoses in office-based rheumatology practice [8; 17]. Fibromyalgia is usually diagnosed between the ages of 20 and 55 years, but the prevalence increases with age, peaking at 70 to 79 years of age (at approximately 7% for women and 1% for men) [5].

The prevalence of fibromyalgia according to race/ethnicity in older studies has been inconclusive, as studies have either included a predominantly white population or have not specified the race/ethnicity of the subjects [13]. In general, the prevalence is similar among racial and ethnic groups [18]. There is no evidence of a higher prevalence of fibromyalgia in industrialized countries and cultures. Among a cohort of 266 individuals with systemic lupus, black race had a negative association with fibromyalgia, and the prevalence has been low among Hispanic and Mexican individuals as well [19; 20].

## PATHOGENESIS

Several etiologies for fibromyalgia have been postulated and explored; the syndrome has been thought to be an inflammatory condition, an autoimmune disease, an unexplained medical syndrome, or a psychiatric condition [3; 7; 8; 21; 22]. However, research has provided little or no evidence to support these bases, and the pathogenesis of the syndrome continues to be poorly understood [8; 9; 23].

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Pioneering sleep studies in the 1970s demonstrated that people with fibromyalgia had abnormal sleep physiology, suggesting a central pathology [24]. Since then, substantial evidence has supported a mechanism of central sensitization, or the amplification of pain in the spinal cord through spontaneous nerve activity, expanded receptive fields, and augmented stimulus responses [4; 5; 6; 9]. Studies have also shown that, compared with healthy individuals, people with fibromyalgia experience pain differently and have physiologically lower pain thresholds [6]. Research has also indicated significant dysregulation of the hypothalamic-pituitary-adrenal axis is found in fibromyalgia [9]. In addition, there may be abnormalities of descending inhibitory pathways, neurotransmitters, or neurohumoral responses; low levels of serotonin and norepinephrine metabolites have been found in the cerebrospinal fluid of individuals with fibromyalgia [5; 6; 9].

Genetics is thought to be a factor in the susceptibility of fibromyalgia. Family clustering has been reported, and the risk for fibromyalgia is eight times higher for first-degree relatives of individuals with the syndrome [25]. Abnormalities in the serotonin transporter gene and the catecholamine-*O*-methyltransferase gene have been identified [5; 9; 26]. These abnormalities affect the metabolism or transport of serotonin and norepinephrine, which decrease the sensitivity of pain-processing systems through the descending central nervous system pain pathways [5].

## POTENTIAL ENVIRONMENTAL RISK FACTORS

As with autoimmune diseases, several environmental risk factors have been thought to act as triggers for the development of fibromyalgia. Because research on the etiology of fibromyalgia is lacking, individuals' perceptions of triggers have been the source of some of the available information [27]. Perhaps as a result, data on the frequency of environmental triggers are conflicting, with some studies showing that half of all cases have a distinct physical or emotional trigger and other studies indicating that three-quarters of cases or more had no triggering event [9; 27; 28].

Psychiatric conditions have long been associated with fibromyalgia, and research suggests that such conditions may precede fibromyalgia and act as a trigger for the disease [6; 8]. In one study, when individuals were asked what they perceived to be a trigger for fibromyalgia, 73% attributed the development of the disease to emotional trauma or chronic stress; 24% noted emotional/physical abuse as an adult or child as a perceived trigger [27].

Injury/trauma and physical illness may also be triggers. Approximately one-third of individuals who attributed fibromyalgia to an environmental trigger noted physical injury (including those from a motor vehicle accident) as the perceived trigger [27]. Acute illness was perceived as a trigger in 27% of individuals in the same survey [27]. Viral infections have been associated with the development of fibromyalgia, and hepatitis C, Epstein-Barr virus, human immunodeficiency virus (HIV), parvovirus, and Lyme disease are thought to be viral triggers, but no causality has been established [6; 9; 28]. Other pain conditions, hyperprolactinemia, and autoimmune diseases have also been reported to be factors [9; 28].

## ASSOCIATION WITH AUTOIMMUNE DISEASES

Several autoimmune diseases have been found in conjunction with fibromyalgia. In a retrospective study of 2,595 cases of fibromyalgia in a nationwide claims database, the likelihood of systemic lupus or rheumatoid arthritis was two to seven times greater than that for controls [29]. Other studies have confirmed an association between fibromyalgia and systemic lupus and rheumatoid arthritis, with reported rates of up to 65% and 57%, respectively [23]. High rates of Sjögren syndrome (up to 50%), and thyroiditis (up to 31%) have also been reported among individuals with fibromyalgia [3; 9; 30]. A small study has suggested that Hashimoto disease and/or subclinical hypothyroidism may be a predisposition to fibromyalgia; signs and symptoms of fibromyalgia were found in nearly one-third of individuals [30].

## CLINICAL MANIFESTATIONS

Chronic, widespread musculoskeletal pain (on both sides of the body for at least three months) is the defining feature of fibromyalgia [1]. This pain is often associated with muscle tenderness (to palpation) adjacent to areas of tendon insertion [3; 31]. In addition, a constellation of other symptoms are common and vary across patients. Most patients complain of stiffness (especially in the morning), fatigue, sleep abnormalities, and difficulties of cognition, such as mental torpor, maintaining attention, and performing tasks that require rapid thought [1; 2; 3; 27; 31; 32; 33; 34].

The likelihood of depression is high among individuals with fibromyalgia [34]. Major depression has been identified in 20% to 62% of individuals with the syndrome [27; 28; 31; 34; 35]. Factors associated with major depression have included younger age, female gender, being unmarried, number of chronic conditions, and limitations in activities [34].

Cognitive dysfunction (often referred to as "fibrofog") affects approximately 40% of individuals [5]. The primary effect is on memory (working, episodic, and semantic), especially when tasks are complex and the individual's attention is divided [36]. Although memory impairment is not as common as many other symptoms, patients have considered them to be among the most troublesome, which is not surprising given that the impairment is equivalent to about 20 years of aging [27; 32; 36]. Attentional control/function is also commonly impaired in individuals with fibromyalgia [36; 37; 38]. Studies have indicated that cognitive dysfunction cannot be attributed solely to symptoms such as depression, anxiety, and sleep problems, but it does seem to be related to the level of pain [36; 37; 38].

## DIAGNOSTIC EVALUATION

Fibromyalgia cannot be diagnosed on the basis of laboratory tests, imaging studies, or pathologic results. As a result, the diagnosis relies on a carefully taken history and comprehensive physical examination. The American Pain Society guideline recommends that the physical examination include a complete joint examination, manual muscle strength testing, and a neurologic examination [4]. The ACR established diagnostic criteria for fibromyalgia in 1990, but the classification system, designed for use in clinical research rather than clinical practice, has many limitations [1; 2; 3; 39].

The lack of objective testing has led to substantial delays in the diagnosis of fibromyalgia, with a diagnosis confirmed only after many visits to healthcare professionals, referrals, diagnostic tests, and several possible diagnoses [5]. Nearly half of individuals with the disease consulted three to six healthcare providers before the diagnosis was made, and 25% saw more than six providers before diagnosis [27]. Physicians also acknowledge diagnostic delay, noting that an accurate diagnosis of a chronic pain disorder (including fibromyalgia) often is not made until after two to three years and consultations with 8 to 13 healthcare professionals [5].

A self-administered questionnaire developed in 2010 may aid in detecting fibromyalgia. The tool, Fibromyalgia Rapid Screening Tool (FiRST), was developed by a group of rheumatologists and pain experts and consists of six questions that can be answered with a yes/no response [40]. A score of five "yes" responses gave the highest rate of correct identification of fibromyalgia patients (87.9%), with a sensitivity of 90.5% and a specificity of 85.7% [40]. FiRST is meant to be used as an initial screening tool, with established diagnostic criteria used to subsequently confirm the diagnosis [40].

The current challenge in diagnosing fibromyalgia stems from many factors, including a wide range and variation in symptoms, a complex differential diagnosis, and difficulty with the established diagnostic criteria.

### RANGE AND VARIATION IN SYMPTOMS

#### What are the three primary manifestations of fibromyalgia?

There is a wide range of symptoms and comorbidities associated with fibromyalgia, and they occur in a variety of combinations and differ in terms of severity. After the three primary manifestations (fatigue, stiffness, and sleep abnormalities), the most common symptoms are headaches (usually migraine), dry mouth, low back pain, and paresthesias (***Table 1***) [1; 3; 27; 31; 32; 33; 34]. In an online survey conducted by the National Fibromyalgia Association (NFA), 19 symptoms, affecting virtually all body systems, were noted by at least 25% of the respondents [27]. Nearly all individuals with fibromyalgia are polysymptomatic [27].

Most individuals with fibromyalgia describe pain as arising from muscles and joints and also have tender skin [3]. Pain is typically axial in distribution, and pain/stiffness usually occurs in the morning and evening [3]. Patients may note a feeling of swelling in the soft tissues, primarily around the joints, but there is no objective evidence of swelling [3; 28]. The American Pain Society recommends using self-reports as the primary source for pain assessment, focusing on such details as [4]:

- Type and quality of pain
- Source
- Location
- Duration
- Time course
- Pain affect
- Effects on quality of life

Several pain assessment tools may be useful in the setting of fibromyalgia (***Table 2***) [9; 22; 41].

Healthcare professionals should also ask about factors that may exacerbate musculoskeletal symptoms, as these symptoms are modulated in approximately 60% to 79% of individuals [1]. Emotional distress has been the most commonly reported exacerbating factor (83%), followed by changes in the weather (80%), sleeping problems (79%), and strenuous activity (70%) [27]. Many other factors are perceived to worsen symptoms, including fatigue, physical inactivity, mental stress, soft-tissue injuries, travel in a car or plane, and work-related conflict [3; 27].

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| COMMON SYMPTOMS OF FIBROMYALGIA | |
|---|---|
| **Symptom** | **Reported Prevalence** |
| Stiffness | 76% to 91% |
| Fatigue | 24% to 90% |
| Sleep abnormalities | 76% |
| Headaches | 47% to 75% |
| Dry mouth | 18% to 71% |
| Low back pain | 67% |
| Paresthesias | 44% to 67% |
| Restless legs syndrome | 32% to 64% |
| Depression | 20% to 62% |
| Irritable bowel syndrome | 36% to 60% |
| Anxiety | 30% to 56% |
| Raynaud phenomenon | 9% to 53% |
| Muscle spasms | 46% |
| Balance problems | 45% |
| Cognitive dysfunction (impaired memory and/or concentration) | 40% |
| Bloating | 40% |
| Sinus problems | 37% |
| Tooth disorders | 32% |
| Jaw pain | 29% |
| Bladder problems | 26% |
| *Source: [1; 3; 5; 22; 27; 28; 31; 32; 33; 34; 35]* | *Table 1* |

| INSTRUMENTS FOR ASSESSMENT OF FIBROMYALGIA-RELATED SYMPTOMS | |
|---|---|
| **Symptom** | **Assessment Tool** |
| Pain | Visual analog scale<br>Brief Pain Inventory<br>Short Form–McGill Pain Questionnaire<br>Daily pain diary |
| Fatigue | Visual analog scale<br>Multidimensional Assessment of Fatigue Instrument<br>Multidimensional Fatigue Inventory<br>Fatigue Severity Scale |
| Sleep | Visual analog scale<br>Medical Outcomes Study Sleep Scale<br>Pittsburgh Sleep Quality Index<br>Sleep Assessment Questionnaire |
| Depression/anxiety | Beck Depression Inventory<br>Patient Health Questionnaire<br>Beck Anxiety Inventory<br>Hospital Anxiety and Depression Scale |
| Quality of life/functional assessment | Fibromyalgia Impact Questionnaire<br>Short Form–36 Health Survey |
| *Source: [9; 22; 41]* | *Table 2* |

| COMORBIDITIES ASSOCIATED WITH FIBROMYALGIA | | |
|---|---|---|
| **Comorbidity** | **Prevalence** | |
| | **Lifetime** | **Current** |
| Any gastrointestinal problem | 72% | 34% |
| Any psychiatric problem | 68% | 39% |
| Depression | 68% | 39% |
| Hypertension | 49% | 35% |
| Any genitourinary problem | 48% | 5% |
| Severe allergies | 41% | 21% |
| Any endocrine problem | 40% | 28% |
| Any lung problem | 37% | 19% |
| *Source: [43]* | | *Table 3* |

Patient assessment must include evaluation of the severity of symptoms most often associated with fibromyalgia, as well as overall quality of life and functional assessment [4; 9; 22]. Most assessment tools used have been validated in other settings and are not fibromyalgia-specific. Healthcare professionals should ask patients about how their symptoms affect their ability to work, as physical limitations and cognitive dysfunction may result in an inability to maintain normal employment [3; 4]. A daily pain diary may also be useful in documenting how pain influences activities of daily living and quality of life [9].

In relating their history, individuals will often focus on the symptoms that are of most concern or that are most troublesome. According to the NFA survey, the most troublesome symptoms were (in descending order): morning stiffness, fatigue, nonrestorative sleep, pain, forgetfulness, poor concentration, difficulty falling asleep, muscle spasms, anxiety, and depression [27]. In another study, 100 individuals with fibromyalgia ranked symptoms slightly differently, but the top five symptoms were similar: pain or physical discomfort, joint pain/aching, fatigue or lack of energy, poor sleep, and cognitive dysfunction [32].

Because of the predominance of fibromyalgia among women, there are few data on the clinical profile for men with the syndrome. The available research points to differences in the clinical presentation according to gender. Women tend to report more symptoms, to describe more symptoms as major problems, and to report greater life interference from pain [8; 18; 42]. Men have noted significantly lower health perceptions and more physical limitations [42]. With regard to specific symptoms, fatigue and sleep disorders are more common among women, with some studies showing a threefold higher rate [8]. "Pain all over" is also more frequently reported by women than men [8]. The most powerful discriminator between women and men with fibromyalgia is the number of tender points [8].

### Comorbidities

Given the broad range of symptoms and conditions found in association with fibromyalgia, it is difficult to differentiate true comorbidities from manifestations of the syndrome itself [43]. For example, irritable bowel syndrome and restless legs syndrome are traditionally thought of as comorbidities but may be part of the overall clinical syndrome [1; 8; 43]. This is true for many autoimmune diseases but particularly for fibromyalgia, which has been described as overlapping with virtually every other unexplained syndrome [7]. In a study in which current and lifetime comorbidities associated with fibromyalgia, rheumatoid arthritis, and systemic lupus were evaluated, fibromyalgia was associated with significantly higher rates of depression and psychiatric conditions, gastrointestinal problems, and severe allergies (***Table 3***) [43].

## COMPLEX DIFFERENTIAL DIAGNOSIS

The multitude of symptoms and comorbidities associated with fibromyalgia add to the complexity of making a differential diagnosis. Many other conditions can mimic widespread pain, and these conditions must be considered in the differential diagnosis (***Table 4***). Although objective testing cannot confirm a diagnosis of fibromyalgia, it can play an important role in ruling out other possible diagnoses. A CBC, ESR, muscle enzymes, liver function studies, and thyroid function tests can help identify other conditions [4]. However, given the high rate of conditions that occur concurrently with fibromyalgia, clinicians must remember that finding another diagnosis does not automatically rule out a diagnosis of fibromyalgia [3]. Differentiating fibromyalgia from other rheumatic diseases and conditions involving widespread pain is especially difficult. Individuals who have widespread pain and fibromyalgia are typically more symptomatic, dysfunctional, and depressed than people who have widespread pain without fibromyalgia [3].

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| DIFFERENTIAL DIAGNOSIS OF FIBROMYALGIA | | |
|---|---|---|
| **Diagnoses to Consider** | **Shared Manifestations** | **Distinguishing Features** |
| Myofascial pain syndrome | Painful, tender areas in the muscles, commonly affecting the axial muscles | Pain arising from trigger points in individual muscles during examination |
| Chronic fatigue syndrome | Chronic pain and fatigue | Low-grade fever, enlargement of lymph glands, continuous subclinical inflammatory process, and acute onset of illness |
| Rheumatoid arthritis | Joint pain/stiffness | Involvement of hands and feet, positive rheumatoid factor (in 80% to 90% of cases), radiographic evidence of joint erosion |
| Systemic lupus erythematosus | Involvement of multiple systems, joint pain | Malar rash, positive antinuclear antibody test |
| Hypothyroidism | Profound fatigue, muscle weakness, mental slowing | Weight gain, hair loss, increased TSH level |
| Polymyalgia rheumatica | Pain/stiffness in sacrohumeral and pelvic girdle | Increased ESR (in 80% to 90% of cases), age older than 65 years, treatment with glucocorticoids resolves symptoms |
| Spondyloarthropathy | Pain in neck, mid-thoracic, anterior chest wall, or lumbar regions | Pain localized to specific spinal areas, radiographic evidence of sacroiliitis, or radiographic changes in vertebral bodies |
| Polyarticular osteoarthritis | Pain in multiple joints | Radiographic evidence of joint degeneration |
| Polymyositis or other myopathies | Muscle weakness | Proximal, symmetrical muscles affected, increased serum levels of muscle enzymes, abnormal findings on EMG testing and on evaluation of biopsy samples |
| Neuropathic pain syndromes | Tingling, numbness | Burning, shooting pain |
| EMG = electromyography; ESR = erythrocyte sedimentation rate; TSH = thyroid-stimulating hormone. | | |
| *Source: [3; 8; 28]* | | *Table 4* |

## DIFFICULTY WITH DIAGNOSTIC CRITERIA

The ACR designed the classification criteria for fibromyalgia for epidemiologic classification but noted that the criteria would also be useful for diagnosis [1]. However, the criteria are used by only about half of rheumatologists in routine practice and are seldom used in the primary care setting [3]. The classification system consists of two criteria: a history of widespread pain and pain in 11 of 18 tender point sites on digital palpation [1]. It has a sensitivity of 88%, a specificity of 81%, and an accuracy of 85%, but several important problems have been identified.

A primary problem with the criteria is the focus on the tender point evaluation, which has been difficult for clinicians, especially primary care providers, to perform correctly [2; 3]. Perhaps equally as problematic is that widespread pain as the only criterion for diagnosis does not seem sufficient, given the broad range of symptoms associated with the syndrome [3]. A third major problem is the lack of a severity scale, which means that an individual with fibromyalgia may not satisfy the diagnostic criteria for the syndrome if symptoms or pain at tender points improve [3]. As a result of these drawbacks, the diagnosis of fibromyalgia often has been symptom-based, and researchers have sought ways to modify the criteria or use alternative approaches [2; 3; 39].

| AMERICAN COLLEGE OF RHEUMATOLOGY DIAGNOSTIC CRITERIA FOR FIBROMYALGIA | |
|---|---|
| **Criteria** | |
| A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:<br>• WPI ≥7 and SSS score ≥5 or WPI 4–6 and SSS score ≥9.<br>• Generalized pain is present, defined as pain in at least 4 of 5 regions (left upper, right upper, left lower, right lower, axial)<br>• Symptoms have been generally present at a similar level for at least three months. | |
| **Ascertainment** | |
| WPI | Note the number areas in which the patient has had pain over the last week. In how many of the following areas has the patient had pain? Score will be between 0 and 19.<br>• Shoulder girdle, left<br>• Shoulder girdle, right<br>• Upper arm, left<br>• Upper arm, right<br>• Lower arm, left<br>• Lower arm, right<br>• Hip (buttock, trochanter), left<br>• Hip (buttock, trochanter), right<br>• Upper leg, left<br>• Upper leg, right<br>• Lower leg, left<br>• Lower leg, right<br>• Jaw, left<br>• Jaw, right<br>• Chest<br>• Abdomen<br>• Upper back<br>• Lower back<br>• Neck |
| SSS score | For the symptoms of fatigue, waking unrefreshed, and cognitive dysfunction, indicate the level of severity over the past week using the following scale:<br>0 = No problem<br>1 = Slight or mild problems, generally mild or intermittent<br>2 = Moderate, considerable problems, often present and/or at a moderate level<br>3 = Severe: pervasive, continuous, life-disturbing problems<br>Considering somatic symptoms[a] in general, indicate whether the patient has:<br>0 = No symptoms<br>1 = Few symptoms<br>2 = A moderate number of symptoms<br>3 = A great deal of symptoms<br>The final score will be between 0 and 12. |
| [a]Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms. | |
| *Source: [221; 222]* | *Table 5* |

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In one study to assess alternative approaches, survey criteria consisting of a Regional Pain Scale score of at least 8 and a fatigue score of at least 6 was found to be concordant with the ACR criteria in 72% of cases [39]. Clinical diagnosis (the clinician's impression irrespective of the ACR criteria) was concordant with the ACR criteria in 75% of cases. The authors concluded that all diagnostic methods have utility [39]. In another study, an effort to modify the criteria to include the three most common symptoms—morning stiffness, sleep disturbances, and fatigue—yielded a sensitivity of 81%, a specificity of 61%, and an accuracy of 72% [3].

To address the problems inherent in its classification system, the ACR published updated diagnostic criteria for fibromyalgia in 2016 [2]. The ACR used a symptom severity scale and the Regional Pain Scale (renamed the Widespread Pain Index) to construct a new case definition of fibromyalgia: a Widespread Pain Index (WPI) score of 7 or greater and a symptom severity score (SSS) of 5 or more OR a WPI score of 4–6 and a SSS of 9 or greater [2]. The WPI has been found to correlate well with findings of the tender point examination, eliminating the need for that examination [2]. The symptoms evaluated by the SSS are fatigue, cognitive dysfunction, and waking unrefreshed (***Table 5***) [2; 44]. In addition, the new criteria minimizes misclassification of regional pain disorders and eliminates the confusing recommendation regarding diagnostic exclusion [44]. Another advantage is that the criteria can demonstrate change in the individual's health status and allows for fibromyalgia to be seen as part of a continuum [2].

## TREATMENT

As with all chronic illnesses, the goal of treatment in fibromyalgia is to reduce symptoms, improve function, and engage the patient's involvement in self-care [22]. Studies have shown that treatment is most effective when it includes the combination of patient education, nonpharmacotherapy approaches (including exercise), and selective pharmacotherapy for persistent symptoms or comorbidities [4; 8; 45; 46; 47; 48].

Treatment guidelines for fibromyalgia have been established by the American Pain Society and EULAR, and subsequent systematic reviews and meta-analyses have provided further findings to support both pharmacologic and nonpharmacologic treatment [4; 46; 49]. Familiarity of guidelines and recommended treatments, especially among primary care providers, is low, and adherence is suboptimal [5; 50]. For example, a substantial number of people with fibromyalgia take pain medications that lack evidence for effectiveness or that are less effective than alternative options [27; 50].

In addition, the practice guidelines for fibromyalgia have many limitations, the most important of which is that their evidence base predates the FDA approval of three drugs for the treatment of the condition. The treatment guidelines may also lack clinical utility because of the crucial need to customize treatment of fibromyalgia according to the unique combination of symptoms in an individual patient. A pooled analysis showed that pain reduction alone does not make people with fibromyalgia feel better; instead, improvements in fatigue, physical functioning, mood, and impact on daily living are important factors in feeling better [51]. These factors must therefore be considered when developing a treatment plan, and optimum treatment will depend on the level of various symptom involvement for the patient [5; 41]. Effective treatment of fibromyalgia may also necessitate guideline-based treatment for comorbidities (e.g., irritable bowel syndrome and restless legs syndrome) [41].

The approach most often used for initial management of fibromyalgia includes patient education and reassurance; an exercise program that combines stretching, aerobic conditioning, and strength training; and selective, low-dose monotherapy aimed at relieving symptoms that do not respond to nonpharmacologic measures.

### NONPHARMACOLOGIC TREATMENT

Nonpharmacologic measures are important components of an effective fibromyalgia treatment plan. Strong evidence has been documented for exercise (aerobic and/or muscle-strength training), cognitive-behavioral therapy, and patient education, and the combination of the three components is recommended as the initial management approach [28; 45; 46; 48].

#### Patient Education

The goal of patient education is to effect a change in the patient's perception of his or her role in managing and coping with symptoms [28]. Patients benefit from an explanation of the disease and reassurance regarding symptoms and prognosis; other topics for discussion are treatment options, sleep hygiene, the importance of conditioning and exercise, and the role of pharmacotherapy for comorbidities such as mood and sleep disorders. There is good evidence that patient education is an essential component of effective treatment [4; 45; 46; 48]. Even a single multidisciplinary educational program was associated with significant improvements in pain, fatigue, morning tiredness, stiffness, anxiety, and depression [45]. Education in a variety of formats has been found to be useful, including lectures, written materials, group discussions, demonstrations, and web-based programs [45; 52]. Healthcare professionals should encourage their patients to take advantage of many reliable online educational resources.

Language, cultural competency, and health literacy are significant issues, given the growing percentages of racial/ethnic populations. According to U.S. Census Bureau data from 2015, more than 40 million Americans are foreign-born, 62 million Americans (21% of the population) speak a language other than English at home, and more than 25 million (8.5% of the population) report that they speak English less than "very well" [84]. Clinicians should ask their patients what language they prefer for their medical care information, as some individuals prefer their native language even though they have said they can understand and discuss symptoms in English [85].

Most important, perhaps, is the fact that clinical consequences are more likely with ad hoc interpreters than with professional interpreters [86]. A systematic review of the literature showed that the use of professional interpreters facilitates a broader understanding and leads to better clinical care than the use of ad hoc interpreters, and many studies have demonstrated that the lack of an interpreter for patients with limited English proficiency compromises the quality of care. The use of professional interpreters improves communication (errors and comprehension), utilization, clinical outcomes, and patient satisfaction with care [87; 88].

**Exercise**

Exercise not only helps to alleviate many fibromyalgia symptoms but also helps to reverse the effects of deconditioning and improve physical fitness [8; 47; 53; 54; 55; 56]. In a study of 207 women who were actively treated with medication for confirmed fibromyalgia, progressive walking, simple strength-training exercises, and stretching activities led to several improvements, including higher scores for functional status, reduced fatigue, better mental health, reduced depression, and greater self-efficacy [53]. The benefits of exercise are enhanced when combined with targeted self-management education [28; 53].

A meta-analysis showed that supervised aerobic exercise training has beneficial effects on physical capacity and symptoms related to fibromyalgia and that strength training may also have benefits on some fibromyalgia symptoms [54]. Another meta-analysis published in 2010 showed that aerobic exercise has a significant positive effect on a variety of disease-related symptoms, with reductions in pain, fatigue, depressed mood, and limitations of health-related quality of life, as well as improved physical fitness [56]. A 2013 Cochrane review found low-quality evidence that resistance training (moderate-to-high intensity) improves functioning, muscle strength, pain, and tenderness in women with fibromyalgia [57]. Other low-quality evidence suggests that aerobic exercise is superior to resistance training for improving pain, but resistance training is superior to flexibility exercise training in women with fibromyalgia for improvements in pain and multidimensional function. Moderate-to-high resistance training is safe for women with fibromyalgia [57].

Both the American Pain Society and EULAR recommend exercise programs as part of treatment for fibromyalgia [46; 58]. The American Pain Society recommends beginning with low levels of exercise and working gradually to a goal of moderately intense aerobic exercise at least two to three times per week [58]. However, fewer than one-third of NFA survey respondents said they engaged in aerobic exercise; more respondents said they participated in "gentle walking" (64%) and stretching (62%), and fewer noted use of physical therapy (24%) or strength training (18%) [27]. Aquatic physical therapy has also been recommended for relief of fibromyalgia-related stiffness [59].

A 2018 report provides evidence that a mind-body treatment approach, specifically a tai chi program, is of equal or greater benefit than standard care aerobic exercise alone [60]. In this blinded, prospective study, 226 adults with fibromyalgia (widespread pain index ≥7 and severity score ≥5) were randomly assigned either to supervised aerobic exercise (24 weeks, twice weekly) or to one of four classic Yang-style tai chi interventions (12 or 24 weeks, once or twice a week). Participants were followed for 52 weeks; the primary outcome was change in the fibromyalgia impact questionnaire scores at 24 weeks compared with baseline. The results showed that improvement in symptom scores was greater for subjects in each of the tai chi groups than for those receiving aerobic exercise. A clinically significant difference was only observed when comparing the highest-intensity tai chi program (twice weekly for 24 weeks) with aerobic exercise. Benefit with respect to secondary outcomes (assessment scores for anxiety, depression, coping strategies, functional limitations, sleep, and quality of life) also favored the tai chi interventions. At 52 weeks the combined tai chi groups continued to show more improvement in primary and most secondary outcomes than the aerobic exercise group.

EULAR notes that exercises should be tailored to the individual patient, and modifications should be made according to the severity of symptoms [46]. For example, a sedentary individual with moderate-to-severe fibromyalgia should begin with breathing, posture, and relaxation training, move to flexibility exercises, then to strength and balance exercise, and finally, to aerobic exercise [55].

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**Cognitive-Behavioral Therapy**

The goal of cognitive-behavioral therapy is to move patients toward more adaptive beliefs about their ability to cope with symptoms, which in turn increases self-management [47]. Cognitive-behavioral therapy is designed to help individuals improve the way they think about fibromyalgia and cope with the overall effects of its symptoms [8]. It is most effective when it focuses on a specific outcome, especially one that is the subject of the patient's maladaptive thoughts and expectations [8; 47].

A systematic review of 23 studies showed that of 30 psychologic treatments for fibromyalgia, cognitive-behavioral therapy was associated with the greatest effect sizes, especially for short-term reduction in pain [61]. In addition to short-term and long-term reductions in pain, cognitive-behavioral therapy has been associated with reductions in sleep disturbances and depression and improvements in functional status [8; 46; 47; 58; 61]. Benefit is typically achieved in 10 to 20 sessions [28]. Despite recommendations for cognitive-behavioral therapy, it may be underutilized. According to the NFA survey, only 8% of respondents had used this strategy [27].

Cognitive-behavioral therapy has been significantly beneficial in many individuals with psychiatric illnesses, such as depression and anxiety disorders, and so may be most useful for individuals with fibromyalgia who have these symptoms [47]. The individuals most likely to respond are probably those who have greater emotional distress, fewer coping skills, or less social support [28; 47].

**Other Approaches**

Relaxation techniques are often part of cognitive-behavioral therapy for fibromyalgia, and their effectiveness is generally accepted, even though direct evidence is lacking [47]. Relaxation/meditation was practiced by 47% of the NFA survey respondents [27]. Mindfulness-based stress reduction therapy has also been evaluated; however, only weak evidence exists for benefit in fibromyalgia [62].

The EULAR guidelines include a recommendation (level IIb) for heated pool treatment, with or without exercise, on the basis of studies showing improvement in pain and function [46]. A subsequent meta-analysis of 10 randomized controlled trials demonstrated moderate evidence that hydrotherapy has short-term beneficial effects on pain and health-related quality of life [63].

The lack of fully effective treatments has led patients—and sometimes their healthcare providers—to explore other options to help manage symptoms. Some of these options have no or weak evidence of effectiveness, and the approaches most commonly used by patients are often not recommended practices. For example, the three interventions used most often by the NFA survey respondents were resting (86%); distraction, such as reading or watching television (80%); and heat modalities, such as warm water or hot packs (74%) [27]. The issue is not that these methods are not helpful, rather that the use rates for these approaches are much higher than for many evidence-based recommended strategies [27].

Among the other approaches patients often try are complementary and alternative medicine; between 40% and 90% of individuals with fibromyalgia have tried at least one such method [27; 50; 64]. However, evidence indicates that most of these methods are ineffective. There is limited evidence to support spinal manipulation [65]. Evidence is also lacking on the effectiveness of herbal, nutritional, and dietary supplements (including St. John's wort, ginseng, valerian, melatonin, and botanical oil) for the symptomatic treatment of fibromyalgia [47; 65; 66]. Despite this, approximately 43% to 68% of people with fibromyalgia use such supplements, although they give low ratings for their effectiveness [27; 50]. Given the high rate of individuals with fibromyalgia who seek symptomatic relief from complementary and alternative methods, the American Pain Society guidelines recommend that clinicians ask their patients about their use of such practices and educate them about their effectiveness and possible negative interactions [4].

Methods with greater evidence of benefit include acupuncture and massage therapy. A 2013 Cochrane review found low-to-moderate level evidence that acupuncture (particularly electro-acupuncture) is effective for the treatment of fibromyalgia symptoms compared with no treatment or standard therapy [67]. Acupuncture in general may relieve pain and stiffness, and electro-acupuncture may improve overall well-being, fatigue, and sleep quality. A 2014 meta-analysis of nine randomized controlled trials found that massage therapy (for at least five weeks) has beneficial immediate effects on improving pain, anxiety, and depression in fibromyalgia patients [68]. However, no follow-up data are available to show long-term benefit. Long-term data are similarly unavailable for qigong, a somewhat popular Chinese medical exercise, but low-quality evidence exists for the short-term improvement of pain, quality of life, and sleep quality and very low-quality evidence exists for improvement of fatigue [69]. Increased psychologic well-being is often reported by qigong practitioners.

| PHARMACOLOGIC TREATMENTS USED IN FIBROMYALGIA | | | |
|---|---|---|---|
| **Drug** | **Dose** | **Common Adverse Events** | **Comments** |
| **Antidepressants** | | | |
| Amitriptyline | 25–50 mg PO at bedtime | Nausea, vomiting, dry mouth, dizziness, drowsiness, headache | Recommended by American Pain Society and EULAR |
| Duloxetine | 60 mg PO daily | Nausea, dry mouth, constipation, drowsiness, decreased appetite | Approved by FDA for fibromyalgia in 2008 |
| Milnacipran | 50–100 mg PO twice daily | Nausea, headache, constipation, dizziness, hot flush, dry mouth | Approved by FDA for fibromyalgia in 2009 |
| **Anticonvulsants** | | | |
| Pregabalin | 300–450 mg PO daily | Diarrhea, dizziness, blurred vision, dry mouth, vomiting | Approved by FDA for fibromyalgia in 2010 |
| Gabapentin | 1,200–2,400 mg PO daily | Viral infections (in children), dizziness, somnolence, ataxia | Limited data on effectiveness |
| **Analgesics/Muscle Relaxants** | | | |
| Cyclobenzaprine | 10–30 mg PO at bedtime | Drowsiness, xerostomia, dizziness | Recommended by American Pain Society |
| NSAIDs | — | — | No evidence to support use, but may be of benefit in treating comorbidities |
| Glucocorticoids | — | — | No evidence to support use, but may be of benefit in treating comorbidities |
| **Opioids** | | | |
| Low-dose (tramadol) | 200–300 mg PO daily | Hot flush, dizziness, headache, constipation, nausea | Recommended by American Pain Society and EULAR |
| Potent | — | — | Not recommended; should be used only if all other approaches have been exhausted |
| **Sedative Hypnotics** | | | |
| Zolpidem | 5–10 mg PO at bedtime | Headache, somnolence, dizziness | Improves sleep; no effect on pain |
| Benzodiazepines and sedatives | — | — | Evidence of effectiveness is lacking |

*Source: [5; 26; 28; 41; 49; 58; 70; 71; 72; 73; 74]* *Table 6*

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## PHARMACOLOGIC TREATMENT

No single drug has been found to manage all fibromyalgia symptoms, and a combination approach is often used [27; 41]. Antidepressants were the first medications used to treat fibromyalgia; drugs in this class include tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) [26; 41]. In general, antidepressants reduce pain through a direct effect rather than an indirect effect mediated by an effect on depression [41]. Other drugs that have been shown to be effective include anticonvulsant drugs, some analgesics/muscle relaxants, and nonbenzodiazepines (***Table 6***) [5; 26; 28; 41; 49; 58; 70].

### Antidepressants

Both the American Pain Society and EULAR found strong evidence (level I) for the use of a tricyclic antidepressant (amitriptyline) for the treatment of fibromyalgia [4; 46]. The American Pain Society recommends using amitriptyline for the initial treatment of fibromyalgia, whereas EULAR notes that any of a number of antidepressants should be "considered" [4; 46]. According to a 2009 meta-analysis, there is strong evidence for an association between treatment with antidepressant medications and reductions in pain, depression, fatigue, sleep disturbances, depressed mood, and a better health-related quality of life for people with fibromyalgia [75]. Treatment with an antidepressant does not completely eliminate pain, but tricyclic antidepressants have been found to be more effective for pain relief than either SSRIs or SNRIs [4; 75]. Amitriptyline was the fifth leading "ever used" drug in the NFA survey (reported by 55% of respondents), with 42% of those using the drug saying it was helpful [27]. In addition, use of prescription antidepressants was the third-highest ranked intervention overall in the survey [27].

Two of the three drugs approved by the FDA are SNRIs: duloxetine and milnacipran [5]. Duloxetine was approved on the basis of two trials. In the first study, duloxetine led to a clinically significant treatment response (at least a 30% reduction in pain severity on the Brief Pain Inventory) in more than half of the study participants [76]. Two doses were evaluated: 60 mg once daily and 60 mg twice daily; both doses were associated with significantly higher response rates than that for the placebo group [76]. Duloxetine also significantly improved function and quality of life. Similar results were achieved with the same doses of the drug in the other study [77]. Neither study showed improvement in sleep; however, duloxetine did not interfere with sleep [41; 49; 76; 77]. The drug was also well tolerated, and nausea was the most common side effect. Given the similarity in response with the two doses of duloxetine, the approval is based on the once-daily dose. A 2014 Cochrane review indicated that there is a lack of efficacy data, but that 60–120 mg daily doses were associated with a greater improvement in mental symptoms than in somatic physical pain [78].

Two studies of milnacipran demonstrated the effectiveness of the drug in achieving a composite endpoint of improvement in scores for pain (30% improvement on a visual analog scale), patient global assessment ("very much" or "much" improved), and physical component of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) (six points) [79; 80]. The studies also evaluated the effect of the drug on pain only (improvement in pain and patient global assessment but not SF-36). Two doses were used: 50 mg twice daily and 100 mg twice daily. In both studies, milnacipran was associated with significant improvements in pain, fatigue, patient global assessment, and physical function [79; 80]. Further follow-up has shown the efficacy to be maintained for 12 months [41]. The drug was well tolerated; the most common side effects were mild-to-moderate nausea and headache, both of which resolved with continued use of the medication [79; 80]. The FDA approved milnacipran at both doses.

A systematic review to compare the effectiveness of the three antidepressants demonstrated several differences [81]:

- Amitriptyline was superior to both duloxetine and milnacipran in reducing pain, sleep disturbances, fatigue, and limitations of health-related quality of life.
- Duloxetine was superior to milnacipran in reducing pain, sleep disturbances, and limitations of health-related quality of life.
- Milnacipran was superior to duloxetine in reducing fatigue.
- No differences in tolerability were found among the three drugs.

### Anticonvulsants

The third FDA-approved drug for the treatment of fibromyalgia is pregabalin, an anticonvulsant agent. Several studies have shown pregabalin to significantly improve pain, patient global assessment, fatigue, and health-related quality of life, as well as sleep disturbances [41; 72; 82]. The effect of the drug has lasted for as long as six months [41]. The drug was well tolerated, with the common side effects being dizziness and sedation, which tended to resolve with time of treatment [41].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Scottish Intercollegiate Guidelines Network, pregabalin (titrated up to at least 300 mg daily) is recommended for the treatment of patients with fibromyalgia.

(https://www.sign.ac.uk/assets/sign136.pdf. Last accessed July 23, 2020.)

**Level of Evidence**: A (At least one high-quality meta-analysis, systematic review, or randomized controlled trial directly applicable to the target population)

Anticonvulsants have been evaluated in several trials, and the American Pain Society found level II evidence for this class of drug, whereas the later EULAR guidelines note level I evidence for pregabalin specifically [4; 46; 49]. Another anticonvulsant drug, gabapentin, has also demonstrated efficacy with respect to pain, patient global assessment, function, and sleep [41; 70; 72]. Gabapentin has not been approved by the FDA to treat fibromyalgia, and the drug is not specifically noted in treatment guidelines [4; 46]. Approximately one-third of the respondents in the NFA survey said they had "ever used" gabapentin, and 46% who had used it considered the drug helpful [27]. The side effect profile of gabapentin is similar to that of pregabalin, but the pharmacokinetic and pharmacodynamic profile is not as favorable [41]. An overview of systematic reviews of anticonvulsants showed that both drugs had a modest effect on pain reduction, and it was not possible to conclude if one drug was better than the other [72]. The long-term safety and efficacy of both drugs is also unknown, and many patients are expected to discontinue therapy due to a high incidence of adverse effects. The overview found no evidence of clinical benefit with any other anticonvulsant, including carbamazepine [72].

### Analgesics

For individuals with fibromyalgia, cyclobenzaprine is most effective in reducing what symptom?

With a primary symptom of pain, fibromyalgia has often been treated with analgesics. According to the NFA survey, acetaminophen, ibuprofen, and naproxen were the top three ever-used medications (94%, 87%, and 66%, respectively) [27]. Slightly more than one-third to about one-half of the survey respondents said that these medications were helpful [27]. In another study, nearly 30% of 434 women with fibromyalgia reported taking NSAIDs [50]. However, with no inflammatory mechanism, fibromyalgia is not expected to respond to NSAIDs, and there is no evidence to support the use of NSAIDs or glucocorticoids as a treatment modality [4; 46]. NSAIDs may be of benefit in relieving pain associated with comorbidities, such as osteoarthritis, rheumatoid arthritis, or systemic lupus, which may account for their high rate of use in the NFA survey [27; 41].

Strong evidence has also been documented for cyclobenzaprine, which has both muscle relaxant and tricyclic antidepressant properties [26; 58; 83]. A systematic review of five randomized controlled trials showed that individuals treated with cyclobenzaprine for fibromyalgia were three times as likely to report overall improvement and to note reductions in symptoms, especially sleep disturbances, than controls [83]. Among the NFA survey respondents, 64% had ever used cyclobenzaprine and 58% of these patients considered the drug to be helpful [27].

Neither the American Pain Society nor EULAR recommend the use of potent opioids for the treatment of fibromyalgia, noting that they should be used only if all other pharmacologic and nonpharmacologic options have been exhausted [4; 46]. The American Pain Society found moderate evidence (level II, III) and EULAR documented level I evidence for tramadol, a mild opioid [4; 46]. The drug is recommended in both guidelines and may be used alone or as an adjunctive measure [41; 46; 58]. The dose of tramadol should be increased slowly over time and should be tapered gradually when discontinued [4]. Caution should be used when prescribing tramadol because of the risk of dependence and abuse [46].

### Sedative Hypnotics

Benzodiazepines and sedatives are not recommended for the treatment of fibromyalgia symptoms [28]. Zolpidem, a short-acting nonbenzodiazepine sedative, has been used to improve sleep in people with fibromyalgia, but because zolpidem does not relieve pain, it is useful only as an adjunct medication, and it has not been included in treatment guidelines for fibromyalgia [4; 41; 46]. Approximately 41% of the NFA survey respondents said they had ever used the drug, and 64% of these individuals considered it helpful [27]. In general, prescription sleep medication was the intervention that respondents considered the most effective of all interventions [27].

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## FOLLOW-UP

Individuals with fibromyalgia should be followed up routinely to assess response to treatment. Follow-up visits also offer an opportunity for healthcare professionals to encourage their patients to comply with pharmacologic and nonpharmacologic treatment. Reinforcement for the need to exercise is especially important, as 68% to 83% of people with fibromyalgia have been found to not engage in aerobic exercise [27; 55]. Rates of exercise among the general population are below optimum, and people with fibromyalgia need added encouragement because of many symptoms that may be perceived as barriers (e.g., fatigue, pain).

One approach to enhance adherence to an exercise program is to begin pharmacologic treatment targeting the most distressing or severe symptoms and then provide education about exercise as symptoms begin to improve [28; 55]. It is especially important to address sleep disturbances and fatigue. In contrast to recommendations for the general population, increasing lifestyle activity is not effective as exercise for individuals with fibromyalgia; instead, clinicians should encourage their patients with fibromyalgia to conserve their energy in daily life in order to have the ability to comply with prescribed exercises [55].

The authors of one review of nonpharmacologic treatment suggest that clinicians use the acronym ExPRESS to follow principles of nonpharmacologic pain management [47]:

- **Ex**: Exercise
- **P**: Psychiatric (i.e., addressing psychiatric comorbidities to help improve pain and disability)
- **R**: Regain function (helping patients pace activities to avoid doing too much on days they feel well)
- **E**: Education (referral to reliable resources)
- **S**: Sleep hygiene
- **S**: Stress management (such as cognitive-behavioral therapy and relaxation techniques)

## PROGNOSIS

Fibromyalgia symptoms will persist in most individuals, but the majority still report that they feel better overall than at the time of diagnosis [8; 28]. Better outcomes have been associated with greater self-efficacy, help-seeking behavior, increased level of exercise, and pacing of activities [28].

**Customer Information/Evaluation insert located between pages 32–33.**

# *Smoking and Secondhand Smoke*

**Includes 5 Pharmacotherapeutic/Pharmacology Hours**

***Audience***
This course is designed for nurses, physicians, and other 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 appears at the end of this course.)

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

***Division Planner***
Jane C. Norman, RN, MSN, CNE, PhD

***Division Planner Disclosure***
The division planner has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

***Accreditations & Approvals***
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NetCE designates this continuing education activity for 10 ANCC contact hours.

This activity was planned by and for the healthcare team, and learners will receive 10 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 5 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

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

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

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 originally marketed in Europe for what ailments?

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].

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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. 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 will also explore 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. As of 2019, the plan was still in development and the FDA was continuing to seek public comment and expert opinion [472; 474].

## PREVALENCE AND ECONOMIC IMPACT OF SMOKING

### How many Americans initiated cigarette smoking in 2016?

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 1.8 million Americans initiated cigarette smoking in 2016, continuing a downward trend noted between 2002 and 2013 (ranging from 1.9 to 2.2 million); 40.6% of these were younger than 18 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 2.8 million in 2011 to 2.4 million in 2016 [13]. In 2016, current use of any tobacco product was highest among American Indians/Alaska Natives (42.6%) followed by persons of two or more races (40.2%), whites (31.3%), blacks (27.8%), Hispanics (22%), and Asians (11.9%) [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 [19]. According to a 2009 study by Ellis and colleagues, 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 after close to two years after implementation of smoke-free workplace legislation [20]. They attribute this finding to the large amounts of people in such small 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 reviewed cotinine levels in New York City nonsmokers, and found that 37.1% had elevated levels [17]. It is thought that this reduction is a result of smoke-free air policies enforced within the previous 10 to 15 years. The researchers also agreed that greater population density and pedestrian exposure continued to contribute to the high number of nonsmokers with elevated cotinine levels [17].

Tobacco use is one of the most expensive addictive behaviors in the United States. In 2015, an estimated 299.9 billion cigarette stick equivalents (based on the weight of 0.0325 ounces of tobacco per cigarette) were consumed in the United States, of which 262.7 billion were cigarettes; the rest were other combustible tobacco products [21]. This accounted for $93.9 billion in national expenditures on cigarettes alone in the 2017 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

### Kreteks, or clove cigarettes, are composed of approximately what percentage of tobacco?

Cigarette smoking is on the decline in the United States, but use of other tobacco products is not [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 to 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].

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 roll-your-own 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 roll-your-own 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 18 years of age or older. The goals of these regulations are to increase public health awareness and, especially, reduce marketing and sales to adolescents, 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.

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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.

In 2017, 2.8% of adults were current e-cigarette users. Adults 25 to 44 years of age have the highest rate of e-cigarette use (22.5%), followed by those 45 to 64 years of age (21.3%), 18 to 24 years of age (18.3%), and older than 65 (11%) [456]. Use is much higher among men (24.8%) than women (14.2%).

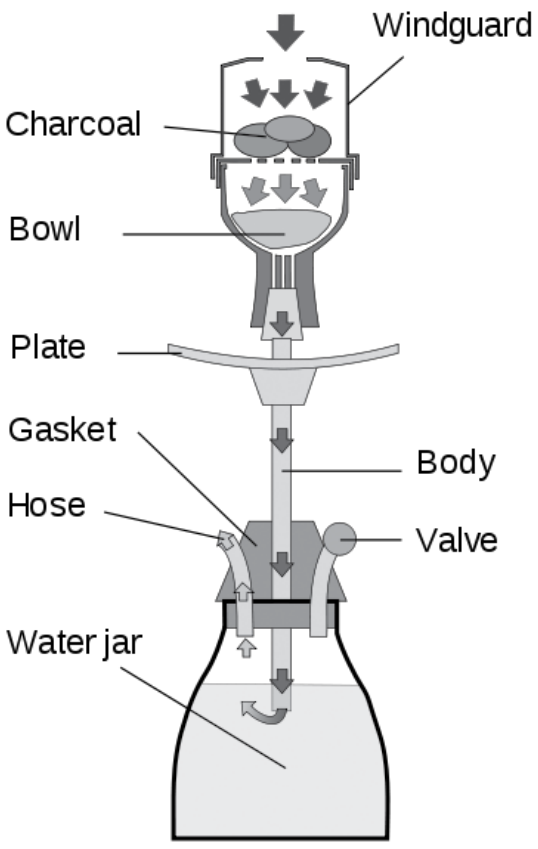
Adolescent use of e-cigarettes has skyrocketed from 1.5% in 2011 to 20.8% in 2018, making it the number one form of tobacco used among youth [459; 465]. In 2018, the FDA issued more than 1,300 warnings and fines to retailers who illegally sold e-cigarette products to minors [464].

According to the Centers for Disease Control and Prevention (CDC), large cigar consumption increased 116% from 2000 to 2017, with cigar smoking being the third most common form of tobacco use among youth [32; 33]. 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].

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.

**SCHEMATIC OF A WATERPIPE**




*Source: [46]* *Figure 1*

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 performs 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 2016, 99.7% of cigarettes sold in the United States had filters, and the FTC reported that 87.9% of the market share of cigarettes had less than 15 mg of tar, 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") 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"

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[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

### What is mainstream 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].

### 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 [71]. 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 are risk factors for the development of a smoking habit?

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 in school-aged children and adolescents.

(http://annals.org/aim/fullarticle/1748857. Last accessed May 13, 2019.)

**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].

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### 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

### Nicotine from cigarette smoke reduces global cerebral blood flow most markedly in what area of the brain?

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].

### PSYCHOLOGIC DEPENDENCE

Many smokers believe that smoking increases 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

##### What percentage of smokers develop COPD?

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].

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**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 55 to 80 years of age who have a 30 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.

(http://annals.org/aim/fullarticle/1809422. Last accessed May 13, 2019.)

**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].

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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 alcoholics 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].

### DRUG ABUSE

Smoking usually precedes illicit 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 an illegal drug 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 an illicit drug and 16 times more likely to use cocaine than those who smoke less frequently. They are also 10 times more likely to use an illicit 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

#### Smoking is highly comorbid with which 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 2016 National Vital Statistics Systems (NVSS) indicated that 7.2% of pregnant women in the United States reported smoking during pregnancy [179]. 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; 179; 180]. A 2010 study showed that as many as 8% of preterm

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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 what permanent effects?

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].

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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 National Heart, Lung, and Blood Institute recommends promoting a smoke-free home environment for all children and reinforcing this message at every encounter, including urgent visits for respiratory problems.

(https://www.nhlbi.nih.gov/node/80308. Last accessed May 13, 2019.)

**Level of Evidence**: A (Well-designed randomized controlled trials or diagnostic studies performed on a population similar to the Guidelines' target population)

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## 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 1,400 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 pro-

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duction. 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 840,678 deaths in the United States in 2016 [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 antiatherogenic 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**

### Active and passive smoking are known to result in what cardiovascular changes?

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].

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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]. It is 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; 331].

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 males exposed to environmental tobacco smoke in their homes, while nonsmoking males 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 females exposed to smoke in their homes, while nonsmoking females 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].

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### 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 2006 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]. More recent 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

### What is the most sensitive biomarker used to confirm the extent of SHS exposure to nonsmokers?

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

### What is 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 2004 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 2001 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].

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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 2008 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

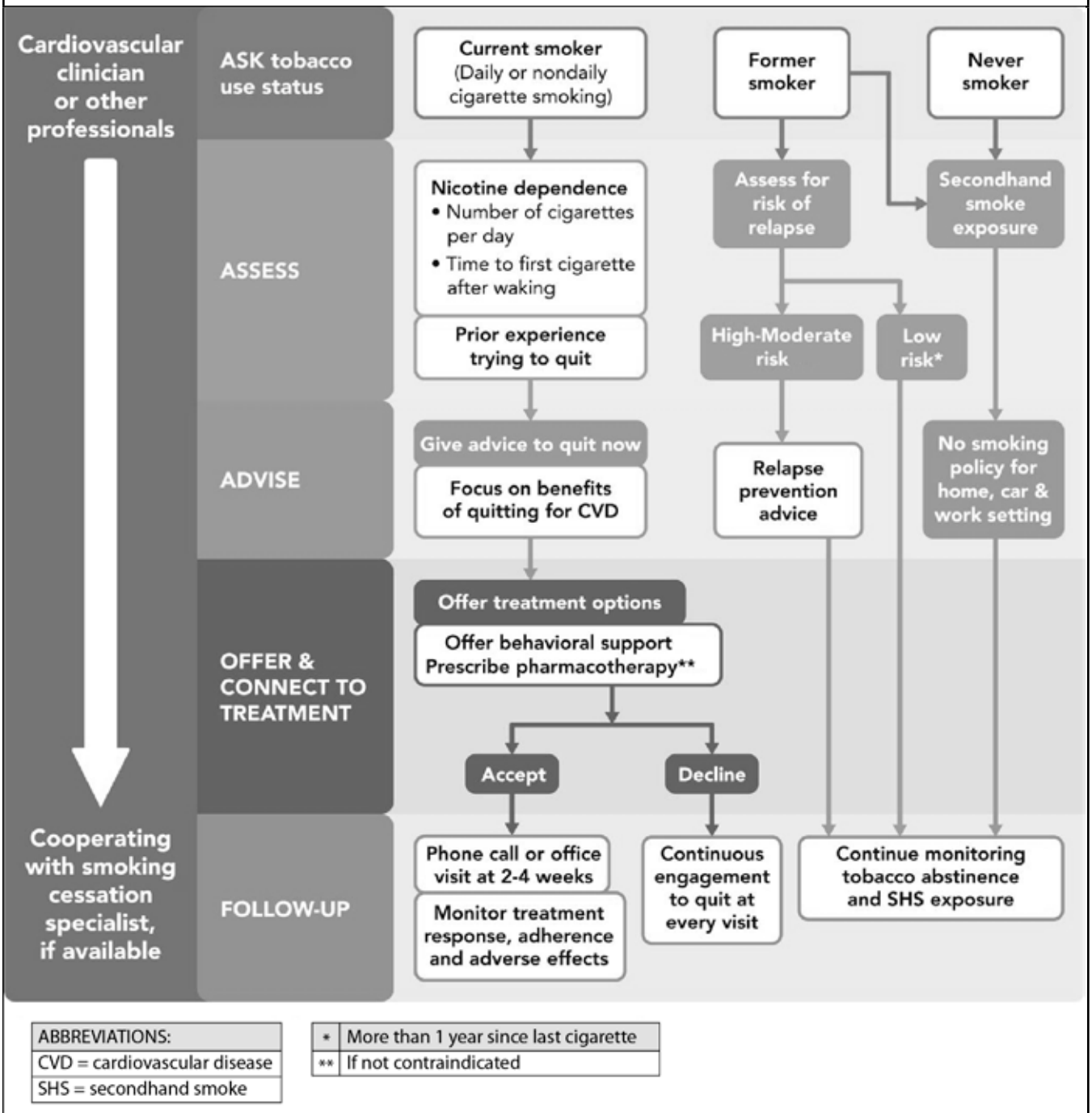
Smoking cessation may be helpful in reducing firsthand and secondhand tobacco smoke exposure by eliminating the source: the smoker(s). Parents and caregivers of young children should receive cessation counseling and/or pharmacotherapy to quit smoking and eliminate the exposure of children to SHS. Parents 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 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.

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 U.S. Food and Drug Administration (FDA)-approved pharmacotherapy for cessation to adults who use tobacco.

(http://annals.org/aim/fullarticle/2443060. Last accessed May 13, 2019.)

**Level of Evidence**: A (There is high certainty that the net benefit is substantial.)

PATHWAY FOR TOBACCO CESSATION TREATMENT




*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*

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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].

According to the University of Michigan Health System, healthcare professionals should advise all tobacco users to seriously consider making a quit attempt using a clear and personalized message. Advice as brief as three minutes is effective.

(https://www.med.umich.edu/1info/FHP/practiceguides/smoking/smoking.pdf. Last accessed May 13, 2019.)

**Strength of Recommendation/Level of Evidence**: IA (Generally should be performed based on randomized controlled trials)

### 5 A's

#### What is the 5 A's approach for intervening with the patient who smokes?

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
- 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].

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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 situations 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**

### Nicotine-replacement therapy is available in what forms?

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 (Chantix), 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; however, medication should be stopped and patients should be reassessed if the intervention has not led to smoking cessation [430; 431]. 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,

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while a meta-analysis study found that combination therapy (varenicline and NRT) was more effective than varenicline alone [434; 435]. Clearly, more clinical trials are necessary to further understand how varenicline compares to bupropion, NRT, and other therapies. Further, patients must be made aware that there are risks of serious neuropsychiatric symptoms with use of varenicline (e.g., suicidal ideation and behavior, worsening of pre-existing psychiatric illness or depressed mood, agitation, and overall changes in behavior) [430].

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].

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].

**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 2017, there were an estimated 34 million adults that smoked cigarettes. 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

### What efforts have been made to regulate tobacco products?

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 public support for increased taxing of tobacco [450]. Since 2002, the average state cigarette tax has increased from 43.4 cents to $1.79 per pack [451; 453; 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. This increase resulted in an 8.3% decline in cigarette sales, one of the largest declines in years, and a continuing downward trend of cigarette sales [452; 453]. As of 2016, the CDC reported an average national retail price of $6.43 per pack of cigarettes [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.

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 are 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 [452; 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.

## FACULTY BIOGRAPHY

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

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

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

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

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## CLINICAL USE OF NEUROMUSCULAR BLOCKING AGENTS

**#35110** • 10 ANCC / 10 Pharm Hours

Book By Mail – $48 • **ONLINE – $40**

**Purpose:** The purpose of this course is to provide intensive care, emergency, and prehospital providers with the clinical knowledge to administer neuromuscular blocking agents in a safe and effective fashion, as well as to know how such agents can be effectively monitored and, ultimately, safely and efficiently reversed.

**Faculty:** Richard E. Haas, RN, MSN, EdM, PhD, CRNA, PHRN, LTC (Retired)

**Audience:** This course is designed for nurses, nurse practitioners, and other allied health professionals in a variety of settings, including the intensive care unit, emergency department, acute care, prehospital settings, critical care, and post-anesthesia care.

**Additional Approval:** AACN Synergy CERP Category A

## DIAGNOSING AND TREATING OVERWEIGHT AND OBESE PATIENTS

UPDATE

**#91573** • 5 ANCC / 2 Pharm Hours

Book By Mail – $28 • **ONLINE – $20**

**Purpose:** The purpose of this course is to educate healthcare professionals about the epidemiology and treatment of overweight and obese patients. Clinical management, presentation, diagnosis, and behavioral and medical management will be reviewed to assist healthcare professionals in encouraging their patients to lose weight and prevent obesity-related comorbidities.

**Faculty:** John J. Whyte, MD, MPH

**Audience:** This course is designed for all physicians, nurses, and social work/counseling groups involved in the care of patients who are overweight or obese.

**Additional Approval:** AACN Synergy CERP Category A

## PRESCRIBING OPIOIDS, PROVIDING NALOXONE, AND PREVENTING DRUG DIVERSION: THE WEST VIRGINIA REQUIREMENT

WV Mandate

**#91602** • 3 ANCC / 3 Pharm Hours

Book By Mail – $23 • **ONLINE – $15**

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

**Faculty:** Mark Rose, BS, MA

**Audience:** This course is designed for all physicians, physician assistants, and nurses in West Virginia who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.

**Additional Approval:** AACN Synergy CERP Category A

**Special Approvals:** This course fulfills the West Virginia Board of Examiners for Registered Professional Nurses requirement for 3 hours of education related to Drug Diversion and Best Practice Prescribing of Controlled Substances.

## AUTISM SPECTRUM DISORDER

UPDATE

**#92203** • 5 ANCC / 1 Pharm Hour

Book By Mail – $28 • **ONLINE – $20**

**Purpose:** The purpose of this course is to provide healthcare professionals with a basic understanding of the very complex, misunderstood, often puzzling, and sometimes disabling condition, enabling them to provide more thorough patient care, recognize symptomatology, and educate patients, families, teachers and communities about autism spectrum disorder.

**Faculty:** Sharon M. Griffin, RN, PhD

**Audience:** This course is designed for healthcare professionals in all practice settings who may be involved in the care of patients with an autism spectrum disorder.

**Additional Approval:** AACN Synergy CERP Category A, CCMC

## PEDIATRIC ABUSIVE HEAD TRAUMA

KY Mandate

**#92403** • 1.5 ANCC Hours

Book By Mail – $23 • **ONLINE – $15**

**Purpose:** The purpose of this course is to raise awareness and provide healthcare providers with the knowledge and skills necessary to quickly and accurately identify pediatric abusive head trauma and to intervene in cases of abuse, which should decrease the morbidity and mortality experienced by the victims.

**Faculty:** Susan Engman Lazear, RN, MN

**Audience:** This course is designed for all healthcare professionals who may intervene to prevent or identify pediatric abusive head injuries.

**Additional Approval:** AACN Synergy CERP Category B

**Special Approvals:** This course is designed to fulfill the Kentucky requirement for 1.5 hours of pediatric abusive head trauma continuing education.

## HYPERTENSION: STRATEGIES TO IMPROVE OUTCOMES

**#94222** • 5 ANCC / 5 Pharm Hours

Book By Mail – $28 • **ONLINE – $20**

**Purpose:** The purpose of this course is to provide healthcare professionals with the information necessary to develop treatment regimens associated with optimal adherence and provide adequate patient education, counseling, and support to patients with hypertension.

**Faculty:** John J. Whyte, MD, MPH

**Audience:** This course is designed for all physicians, physician assistants, nurses, and pharmacy professionals involved in the care of patients with hypertension.

**Additional Approval:** AACN Synergy CERP Category A, CCMC

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# Course Availability List *(Cont'd)*

## AUTOIMMUNE DISEASES

UPDATE

**#94453** • 15 ANCC / 10 Pharm Hours

Book By Mail – $68 • **ONLINE – $60**

**Purpose:** The purpose of this course is to provide healthcare professionals with the information necessary to diagnose and treat the most common autoimmune disorders according to evidence-based or guideline-endorsed recommendations in order to improve patient quality of life.

**Faculty:** Lori L. Alexander, MTPW, ELS, MWC

**Audience:** This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the diagnosis, treatment, and care of patients with autoimmune diseases.

**Additional Approval:** AACN Synergy CERP Category A, CCMC

## PNEUMONIA

**#94672** • 10 ANCC / 5 Pharm Hours

Book By Mail – $48 • **ONLINE – $40**

**Purpose:** The purpose of this course is to provide members of the healthcare team with the knowledge and skills necessary to appropriately diagnose, treat, and prevent pneumonia.

**Faculty:** Carol Whelan, APRN; Lori L. Alexander, MTPW, ELS, MWC

**Audience:** This course is designed for all physicians, physician assistants, and nurses, especially those working in the emergency department, outpatient settings, pediatrics, nursing homes, and intensive care units.

**Additional Approval:** AACN Synergy CERP Category A, CCMC

## ANTIBIOTICS REVIEW

UPDATE

**#95073** • 5 ANCC / 5 Pharm Hours

Book By Mail – $28 • **ONLINE – $20**

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

**Faculty:** Donna Coffman, MD

**Audience:** This course is designed for healthcare providers who prescribe and administer antibiotics to patients.

**Additional Approval:** AACN Synergy CERP Category A

## RESPONSIBLE AND EFFECTIVE OPIOID PRESCRIBING

Pain Management/ Controlled Substance

**#95151** • 3 ANCC / 3 Pharm Hours

Book By Mail – $23 • **ONLINE – $15**

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

**Faculty:** Mark Rose, BS, MA

**Audience:** This course is designed for all HCPs who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.

**Additional Approval:** AACN Synergy CERP Category A, CCMC

**Special Approvals:** This course is designed to meet the requirement for opioid/substance abuse education. This course meets the Kentucky requirement for 1.5 hours related to KASPER, pain management or addiction.

## MEDICAL MARIJUANA AND OTHER CANNABINOIDS

**#95172** • 5 ANCC / 5 Pharm Hours

Book By Mail – $28 • **ONLINE – $20**

**Purpose:** The purpose of this course is to provide healthcare professionals with unbiased and evidence-based information regarding the use of marijuana and other cannabinoids for the treatment of medical conditions.

**Faculty:** Mark Rose, BS, MA

**Audience:** This course is designed for healthcare professionals in the primary care setting involved in the care of patients who use or who are candidates for the therapeutic use of marijuana or other cannabinoids.

**Additional Approval:** AACN Synergy CERP Category A, CCMC

## ALZHEIMER DISEASE

MA Mandate

**#96153** • 15 ANCC Hours

Book By Mail – $68 • **ONLINE – $60**

**Purpose:** The purpose of this course is to provide clinicians with the skills to care for patients with Alzheimer disease in any setting as part of the interdisciplinary team.

**Faculty:** Joan Needham, MSEd, RNC

**Audience:** This course is designed for clinicians who come in contact with patients with Alzheimer disease in hospitals, long-term care facilities, home health care, and the office.

**Additional Approval:** AACN Synergy CERP Category A, CCMC

**Special Approvals:** This course meets the one-time Massachusetts requirement for education in the diagnosis, treatment, and care of patients with cognitive impairments.

## ANXIETY DISORDERS

**#96181** • 15 ANCC / 10 Pharm Hours

Book By Mail – $68 • **ONLINE – $60**

**Purpose:** The purpose of this course is to provide healthcare professionals with the knowledge and skills necessary to appropriately identify and treat patients with anxiety disorders, addressing knowledge gaps, enhancing clinical skills, and improving patient outcomes.

**Faculty:** Mark Rose, BS, MA

**Audience:** This course is designed for health and mental health providers involved in the identification, treatment, and care of patients with anxiety disorder.

**Additional Approval:** AACN Synergy CERP Category A, CCMC

## MENTAL HEALTH ISSUES COMMON TO VETERANS AND THEIR FAMILIES

WV Mandate

**#96341** • 2 ANCC Hours

Book By Mail – $23 • **ONLINE – $15**

**Purpose:** The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of military service on patient health as well as the skills necessary to effectively identify and intervene for these patients.

**Faculty:** Alice Yick Flanagan, PhD, MSW; Mark Rose, BS, MA

**Audience:** This course is designed for physicians, nurses, psychologists, social workers, therapists, counselors, and other healthcare professionals who may treat veterans or their family members.

**Additional Approval:** AACN Synergy CERP Category A, CCMC

**Special Approvals:** This course is designed to meet the West Virginia requirement for 2 hours of education on mental health conditions common to veterans and family members of veterans.

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# Course Availability List *(Cont'd)*

## SUICIDE ASSESSMENT AND PREVENTION

**#96441** • 6 ANCC Hours

Book By Mail – $32 • **ONLINE – $24**

**Purpose:** The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of depression and suicide on patient health as well as the skills necessary to identify and intervene for patients at risk for suicide.

**Faculty:** Mark Rose, BS, MA

**Audience:** This course is designed for physicians, nurses, pharmacists, and other healthcare professionals who may identify persons at risk for suicide and intervene to prevent or manage suicidality.

**Additional Approval:** AACN Synergy CERP Category A, CCMC

## OPIOID USE DISORDER

Controlled Substances/ Addiction

**#96963** • 10 ANCC / 10 Pharm Hours

Book By Mail – $48 • **ONLINE – $40**

**Purpose:** Practice guidance for opioid use disorder in primary care has not kept pace with rapid, profound changes in this area, leaving healthcare professionals with outdated and incomplete information to guide the clinical management of opioid use disorder and related morbidity. The purpose of this course is to close this gap to allow healthcare professionals to provide the best, evidence-based care to patients with opioid use disorder.

**Faculty:** Mark Rose, BS, MA

**Audience:** This course is designed for medical and mental healthcare providers, including physicians, nurses, pharmacy professionals, social workers, and counselors/therapists who may be involved in identifying or treating opioid use disorder

**Additional Approval:** AACN Synergy CERP Category A, CCMC

**Special Approvals:** This course meets the Kentucky requirement for 4 hours of addiction, which includes 1.5 hours of addiction pharmacology. This course meets the Massachusetts requirement for controlled substances, and the Virginia requirement for 2 hours in controlled substances.

## DOMESTIC VIOLENCE: THE KENTUCKY REQUIREMENT

KY Mandate

**#97913** • 3 ANCC Hours

Book By Mail – $23 • **ONLINE – $15**

**Purpose:** The purpose of this course is to enable Kentucky healthcare professionals in all practice settings to define domestic violence and identify those who are affected by domestic violence. This course describes how a victim can be accurately diagnosed and identifies resources available for domestic violence victims.

**Faculty:** Marjorie Conner Allen, BSN, JD; Alice Yick Flanagan, PhD, MSW

**Audience:** This course is designed for all Kentucky healthcare professionals who may intervene to protect victims of domestic violence.

**Additional Approval:** AACN Synergy CERP Category B

**Special Approvals:** This course is designed to meet the Kentucky requirement for 3 hours of domestic violence. This course meets 3 of the 5 hours for the Kentucky requirement for sexual assault education for those who hold a SANE credential.

## HERBAL MEDICATIONS: AN EVIDENCE-BASED REVIEW

UPDATE

**#98393** • 10 ANCC / 10 Pharm Hours

Book By Mail – $48 • **ONLINE – $40**

**Purpose:** Considering the pharmacological interactions between herbal medications (HMs) and conventional medications, it is paramount to increase the awareness and knowledge of healthcare professionals about HMs. The purpose of this course is to increase healthcare professionals' awareness of the potential risks and benefits of HMs from an evidence-based perspective and promote the planned inclusion of HM use in patients' medical history. This course should allow healthcare professionals to discuss HMs in a knowledgeable and succinct manner with patients and colleagues.

**Faculty:** A. José Lança, MD, PhD

**Audience:** This course is primarily designed for physicians, pharmacists, and nurses. However, considering the widespread availability and increased use of herbal medications, other healthcare professionals, including social workers and clinical therapists, will also benefit from this course.

**Additional Approval:** AACN Synergy CERP Category A

## GERIATRIC POLYPHARMACY

**#99021** • 5 ANCC / 5 Pharm Hours

Book By Mail – $28 • **ONLINE – $20**

**Purpose:** The purpose of this course is to provide clinicians with the knowledge necessary to ensure that geriatric patients are effectively treated while reducing unnecessary polypharmacy.

**Faculty:** Susan Waterbury, MSN, FNP-BC, ACHPN

**Audience:** This course is designed for advanced practice nurses, nurses, pharmacists, pharmacy technicians, and allied healthcare professionals who work with the geriatric population.

**Additional Approval:** AACN Synergy CERP Category A, CCMC

## AGING AND LONG-TERM CARE

**#99353** • 3 ANCC Hours

Book By Mail – $23 • **ONLINE – $15**

**Purpose:** The purpose of this course is to provide the tools necessary for social workers, counselors, mental health professionals, and allied health professionals to successfully assess and care for older adults, an increasingly large portion of the U.S. population.

**Faculty:** Alice Yick Flanagan, PhD, MSW

**Audience:** This course is designed for nurses, social workers, counselors, mental health professionals, and allied health professionals involved in the care of older adults.

**Additional Approval:** AACN Synergy CERP Category B, CCMC

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| ✓ | Course # | Course Title / Contact Hours | Price |
|---|---|---|---|
| | 97280 | Pain Management Pearls: Opioids and Culture / 2 Contact Hours | $15 |
| | 94300 | Fibromyalgia / 3 Contact Hours | $15 |
| | 91783 | Smoking and Secondhand Smoke / 10 Contact Hours | $40 |

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|---|---|---|---|
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Signature

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# Evaluation

(Completion of this form is mandatory)

GKY21

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***Please answer all of the following questions and provide your signature at the bottom of this page.***
***Your postmark or facsimile date will be used as your completion date.***

**Please read the following questions and choose the most appropriate answer for each course completed.**

1. Was the course content new or review?
2. How much time did you spend on this activity?
3. Would you recommend this course to your peers?
4. Did the course content support the stated course objective?
5. Did the course content demonstrate the author's knowledge of the subject?
6. Was the course content free of bias?
7. Before completing the course, did you identify the necessity for education on the topic to improve your nursing practice?
8. Have you achieved all of the stated learning objectives of this course?
9. Has what you think or feel about this topic changed?
10. Did study questions throughout the course promote recall of learning objectives?
11. Did evidence-based practice recommendations assist in determining the validity or relevance of the information?
12. Are you more confident in your ability to provide nursing care after completing this course?
13. Do you plan to make changes in your nursing practice as a result of this course content?

**#97280**
Pain Management Pearls
2 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

**#94300**
Fibromyalgia
3 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

**#91783**
Smoking & Secondhand Smoke
10 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#97280 Pain Management Pearls: Opioids and Culture — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

_____

#94300 Fibromyalgia — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

_____

#91783 Smoking and Secondhand Smoke — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

_____

May we contact you later regarding your comments about these activities? ☐ Yes ☐ No

I have read the course(s) and completed the Evaluation(s) in full.
I understand my postmark or facsimile date will be used as my completion date.

Signature _____

***Signature required to receive continuing education credit.***

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