TECHNICAL REPORT

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Nicotine and Tobacco as Substances of Abuse in Children and Adolescents

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Nicotine is the primary pharmacologic component of tobacco, and users of tobacco products seek out its effects. The highly addictive nature of nicotine is responsible for its widespread use and difficulty with quitting. This technical report focuses on nicotine and discusses the stages of use in progression to dependence on nicotine-containing products; the physiologic characteristics, neurobiology, metabolism, pharmacogenetics, and health effects of nicotine; and acute nicotine toxicity. Finally, some newer approaches to cessation are noted.

INTRODUCTION

Tobacco exposure, whether through personal use, second- or thirdhand smoke exposure, or unintentional exposure, is the most important preventable cause of illness, disability, and death among adults in the United States.[1] Worldwide, tobacco use is also the leading cause of preventable death.[2] Many preventive measures have increased the perceived risk of smoking, which, along with the decreased access to cigarettes, has contributed to a gradual decline in use. However, the rate of decline has begun to slow for the use of cigarettes, and use has increased significantly for nicotine products such as hookahs and electronic nicotine delivery systems as well as for smokeless tobacco. As reported by the Centers for Disease Control and Prevention,[2] e-cigarette experimentation and recent use among US middle and high school students doubled from 2011 to 2012 and has increased significantly since then. It is now estimated that 1.78 million students have ever used e-cigarettes. Of these, 9% (an estimated 160 000 students) have never used conventional cigarettes. The Monitoring the Future Study has also found that more teenagers report using electronic nicotine delivery systems in the past 30 days than any other tobacco product.[3] Although these delivery systems may reduce exposure to some of the toxic chemicals in cigarettes, there are additional toxins associated with electronic nicotine delivery systems, and exposure to nicotine and its high addiction potential remain major concerns.[4]

abstract

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It is well known that tobacco products contain more than 4000 different chemicals.[5] Their effects, along with the sensory stimulation and the conditioning that develops with continued use, may contribute to the addiction process, but nicotine is the major contributor to the development of dependence. It is the primary pharmacologic component of tobacco, and its effects are sought after by users. Its highly addictive nature is responsible for the widespread use and difficulty with quitting.

HISTORICAL BACKGROUND

Nicotine was originally isolated from the herbaceous plant *Nicotiana tabacum,* a native of tropical and subtropical America but now commercially cultivated worldwide. The plant was named after the diplomat Jean Nicot de Villemain, who, in 1556, brought tobacco seeds and leaves as a "wonder drug" to the French court from Brazil.[6] Nicotine is a potent parasympathomimetic alkaloid and is now known to occur in the nightshade family of plants (*Solanaceae*). It is also present in minimal quantities in tomato, potato, eggplant (aubergine), green pepper, and cocoa leaves.[7] Nicotine is produced in the roots and accumulates in the leaves of the tobacco plant, with the amount varying with position: that is, leaves harvested from higher stalk positions contain more nicotine than those from lower positions. Flue curing of the leaves changes the pH so that the smoke of the leaves is better inhaled and, as a result, both more addictive and more toxic. Leaves are usually combined so that, on average, cigarettes (in any of 15 different cigarette brands) contain approximately 1.5% nicotine by weight.[8] Burning tobacco releases the nicotine, which is carried proximally on tar droplets and in the vapor when inhaled. Other alkaloids constitute 8% to 12% of the total alkaloid content of tobacco products.

CRITERIA FOR DEPENDENCE

Both the World Health Organization, in its *International Classification of Diseases*,[9] and the American Psychiatric Association, in its *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*,[10] have issued diagnostic criteria to assess addiction. Currently, "substance use disorder" is the preferred term and includes dependence and withdrawal symptoms. Nicotine meets the established criteria for a drug that produces the symptoms of addiction, specifically, dependence, withdrawal, and craving.

First use of tobacco most often occurs in young adolescents, and the earlier one begins, the less likely one is to be able to stop using tobacco products[11] and the more likely use will continue with greater quantities.[12] It has been estimated that two-thirds of children who smoke in sixth grade become regular adult smokers and almost half (46%) of smokers in the 11th grade become regular adult smokers.[13] Even infrequent experimentation with smoking cigarettes can increase the risk of becoming a regular adult smoker; regular (defined as smoking at least monthly) smoking by an adolescent has been found to increase the risk of becoming an adult regular smoker by 16 times compared with nonsmoking adolescents.[13] Of tobacco-dependent adults, 90% started smoking before 18 years of age and 99% started smoking before 26 years of age.[14]

A number of researchers have studied the development of nicotine addiction in adolescents. Even before any experimentation, adolescents' exposure to advertising and the marketing of the range of tobacco products available can influence their attitudes about the risks and benefits of tobacco use. This initial preparatory stage is when individuals develop attitudes and beliefs about the utility of tobacco and may then begin to experiment with a few cigarettes. A few will never use again, and some will smoke repeatedly but irregularly.

Traditional theoretical models explaining nicotine addiction maintain that, beyond the role of nicotine as a key component required for the development of addiction, other behavioral, social, environmental, and psychological factors are also important for the development and maintenance of addiction.[15] These include the attitude and behavior of friends and family members toward smoking, an underestimation of the addictive potential of nicotine, and an overestimation of the prevalence of peer smoking. Users also report that smoking alleviates anxiety, depression, and pain and that they, therefore, use it as a stress reliever. Although some of these effects may be related to the pharmacologic response along with the relief of withdrawal symptoms at times of smoking cessation, the belief that they are coping better with stress is a psychological effect that may lead to further use to control mood. Frequent dosing of nicotine is associated with hand-to-mouth movement that often becomes a social crutch that is difficult to do without after quitting. Other rituals associated with a particular device used may contribute to continued use. Smoking also becomes connected to specific times, experiences, and events, referred to as cues, and these become reinforcing of use over time. Light or intermittent smokers may be more influenced by these associated activities, such as after eating or drinking alcohol, than the need to use tobacco to relieve withdrawal symptoms.[16]

More recently, a newer model, the sensitization-homeostasis model, has been proposed as an alternative model, and a number of studies have supported this model to explain the development of nicotine addiction in

adolescents.[17] This model suggests that, for adolescents, even infrequent smoking, such as at monthly intervals, is enough to put the individual at risk of dependence.[18,19] With nondaily smoking, even after the first cigarette, early symptoms of dependence, such as wanting to smoke or craving a cigarette, can develop if adolescents go too long without a cigarette.[20] One study has shown that monthly smoking can increase the likelihood of developing dependence by 10-fold.[21] These researchers also found that there is a reciprocal relationship between diminished autonomy about smoking and the frequency of smoking. They suggest that the urge to smoke occurs early on after initiation and that this, in turn, drives the teenager to increase the frequency of smoking, which increases the risk of further dependence symptoms, such as a need to smoke. With increased frequency, the adolescent is more likely to experience a more rapid progression to addiction and the need for daily smoking, such as one would see in a dose-response effect.

Researchers have also found that symptoms of dependence develop in a predictable sequence, beginning with wanting to smoke, followed by craving, and eventually needing to smoke to avoid withdrawal or abstinence symptoms, suggesting that the adolescent has neurophysiologic dependence.[22] Neurophysiologic dependence may lead to tolerance, with a diminished effect experienced with continued use, resulting in an increased amount of nicotine needed to maintain equilibrium. This neuroadaptation within the brain may explain why teenagers report the need for nicotine to function normally.

PHYSIOLOGIC CHARACTERISTICS: FORMULATIONS, PREPARATIONS, AND ABSORPTION

Nicotine is a weak base, and its absorption across biological membranes is pH dependent. It does not rapidly cross membranes in an acidic environment when it is in an ionized form. The predominant form of tobacco in American cigarettes is flue cured. The initial puffs from these cigarettes have an acidic pH resulting in almost completely ionized nicotine that has little if any absorption across the buccal membranes. Air-cured tobacco, the predominant form in pipes, cigars, and a few European cigarettes, is alkaline. The released nicotine is largely nonionized and thus well absorbed through the mouth. Chewing tobacco, snuff, and nicotine polacrilex gum are also of alkaline pH, facilitating absorption through the oral mucous membranes. Nicotine can be absorbed through the skin, and toxicity has been documented in tobacco field-workers and those with skin contact with pesticides containing nicotine. In the lungs, the large surface area provided by the small airways and the alveoli as well as the local physiologic (slightly alkaline) pH of 7.4 allow for the rapid absorption of nicotine from cigarette smoke, where it reaches the systemic circulation without first passing through the liver. It is estimated to reach the brain in as little as 7 seconds after inhalation.[23] The rapid onset of action with inhaled nicotine leads to a greater "high" and reinforces use, which leads to neuroadaptation, and continued use is related not only to the need to obtain nicotine but also to conditioning. Nicotine is poorly absorbed from the stomach because of the acidic pH but well absorbed from the small intestine. Reabsorption from the intestine may be a potential source for enterohepatic circulation.

The dose of nicotine delivered cannot be determined solely by the nicotine content of the product because of these complexities. In addition, when smoking cigarettes, the actual amount of any alkaloid delivered depends on the puffing characteristics: that is, the depth of the puff and the frequency. Smokers typically take 10 puffs within the span of 5 minutes and absorb 1 to 2 mg of nicotine (range: 0.5–3 mg).[24] The elimination half-life of nicotine is 2 to 3 hours, meaning that the level of nicotine in the blood decreases by one-half after a smoker stops smoking for that length of time. This elimination half-life will decrease with repeated exposures to nicotine.

INCREASING PALATABILITY

Several additives are used in the manufacture of cigarettes to reduce the harshness of the smoke.[25] Menthol is an additive that is actively promoted by the tobacco industry for its perceived sensory benefits. A large number of young people and occasional users of cigarettes use menthol cigarettes because it helps reduce harshness. The specific candylike taste of menthol and its cooling, anesthetic, and analgesic properties make it appealing to these smokers.[26] The sensory effects of menthol serve as conditioned stimuli, increasing the reinforcing effects of nicotine and thus the addiction potential of menthol cigarettes. As users become tolerant of this flavor, some actively seek even stronger sensory attributes in a cigarette, and beginning with a menthol-containing product may facilitate an adolescent's progression to daily smoking. Smokers who prefer and choose menthol-containing products tend to be disproportionately black and male.[25] The perceived reduction in harshness may result in the intake of more cigarettes, and therefore more toxic and dependence-causing substances, increasing the difficulty in quitting cigarette use.[27] The perceived reduced harshness also contributes to the perception that cigarettes are less harmful than they actually are.

Similarly, other products have additives that increase their

palatability. The tobacco used in hookahs (shisha, maassel, tumbak, or jurak) is moist and shredded. It is mixed with sweeteners such as honey, molasses, or fruit, and many have candy or fruit flavoring added. Bidis, hand-rolled, thin, filterless cigarettes, are sold unflavored or flavored (eg, with vanilla, strawberry, or mango). Kreteks, clove-flavored cigarettes, have a particularly pungent smell. Kreteks, used in Indonesia, contain eugenol, which has an anesthetic effect, allowing for deeper inhalation. Chewing tobacco is used all over the world; and in 1 form used in India, referred to as pan masala, areca nuts, slaked lime, and other flavoring agents and sweeteners are added. Electronic nicotine delivery systems also have >7760 unique flavors, including fruit, candy, and dessert flavors, raising concerns about the strong appeal of all these products to children.[28]

MECHANISM OF ACTION: NEUROBIOLOGY

Nicotine acts on nicotinic acetylcholine receptors (nAChRs) in the peripheral nervous system (autonomic ganglia and adrenal medulla; neuromuscular junction) and the central nervous system (CNS). The nAChRs are ligand-gated ion channels made up of 5 subunits that assemble around an ion pore. When nicotine or acetylcholine binds, a change occurs in their conformation that renders the ion pore permeable to cations, which, in turn, excite the cell. There are 12 isoforms, 9 α-subunits labeled from α2 to α10 and 3 β-subunits labeled from β2 to β4. The mix of these subunits in each receptor gives the receptor its distinct pharmacologic properties and its response to nicotine stimulation. The activation of some receptors promotes the reinforcing effects, whereas the activation of others limits reinforcement and possibly mediates the aversive effects. An understanding of these subunits is helping researchers develop antismoking medications. In the human brain, the most widely expressed nAChR is the α4,β2 subunit, which has a central function in the mediation of the physiologic effects of nicotine. With repeated exposure, there is an increase in the number of nAChRs. This upregulation is believed to be the response to nicotine-mediated desensitization of the receptors and may play a role in the development of dependence. Overnight, when these receptors become unoccupied, it has been suggested that they recover to a responsive state, which creates the craving and withdrawal symptoms experienced by many in the morning.

Functional imaging studies of the brain have detected differences in brain structure between smokers and nonsmokers. Smokers have been found to have differences in the microstructural order in white matter areas of the brain, specifically the anterior cingulate bundle.[29] Studies also have found that smokers reporting more subjective symptoms of dependence, by using standardized measures, had a decreased density of neural connections, or streamlines, between the anterior cingulate bundle and the precuneus and increased connections between the anterior cingulate bundle and the superior-frontal cortex. These areas of the brain and specific circuits are those correlated with memory, motivation, executive function, and mood. These studies support the connection between subjective symptoms of nicotine dependence and white matter structure and suggest that nicotine dependence over time can result in neuroplastic changes in a number of brain systems.

In addition, various neurotransmitters are involved, including acetylcholine, dopamine, noradrenaline, serotonin, glutamate, opioids, and γ-aminobutyric acid; and the overall physiologic effect of nicotine may result from the interactions of these various neurotransmitters. Nicotine receptors in the CNS are located mainly in presynaptic membrane, and in that way, they regulate the release of several neurotransmitters. Nicotine increases concentrations of dopamine, a neurotransmitter essential for boosting attention, reward-seeking behaviors, and the risk of various addictions, from gambling to drug use.[30] Dopamine is released in the mesolimbic system, the corpus striatum, and frontal cortex and is critical for the drug-induced reward effect. Nicotine receptors in the striatum, where movements are planned and controlled, are located near the terminals that regulate and emit dopamine. In animal studies, even a small dose of nicotine stimulates the release of dopamine in the striatum, stopping movements that otherwise would go uncontrolled. This finding has led to research examining the role of nicotine in the prevention and treatment of a variety of neurologic disorders, including Parkinson disease, mild cognitive impairment, Tourette syndrome, schizophrenia, and attention-deficit/hyperactivity disorder. The available research suggests that youth with mental illness are at increased risk of tobacco use.[31] The direction of causation remains unclear.

Epidemiologic studies have contributed to the development of the gateway drug model that suggest that previous use of the legal drugs tobacco and alcohol increases the vulnerability to the subsequent use of illicit drugs. Studies indicate that ethanol potentiates the response of high-affinity nAChRs to both acetylcholine and nicotine.[32] Even small amounts of alcohol are known to boost nicotine effects, inducing subjects to smoke more. A recent study in a mouse model examining the effects of nicotine on cocaine abuse has provided a

biological mechanism to support the gateway theory by showing that nicotine increases the expression of the FosB gene (which has been related to addiction) and increases the vulnerability to cocaine dependence.[33] This finding suggests that the prevention and cessation of nicotine use may decrease the future risk of addiction to illicit drugs.

NICOTINE METABOLISM

Nicotine is mainly metabolized by the liver (85%–90%), and the metabolites are then excreted through the kidneys. Only 10% of nicotine is excreted unchanged. Nicotine metabolism involves a 2-step process mediated by the cytochrome P450 system, mainly by the hepatic enzymes CYP2A6 and CYP2B6. The first step produces the metabolite cotinine, which is then converted to multiple products, the most abundant being 3′-hydroxycotinine. The ratio of 3′-hydroxycotinine to cotinine is a reflection of in vivo nicotine clearance and is referred to as the nicotine metabolic rate. Some data from patients with chronic kidney disease indicate that the excretion of cotinine is minimally affected.[34]

Cotinine has a long half-life (18–20 hours), and on average, it takes approximately 72 hours to eliminate 90% of the cotinine.[35] Although this long half-life makes it difficult to assess the most recent cigarette intake/smoking pattern, cotinine's concentration in the urine correlates well with blood concentration. The measurement of urinary cotinine concentration is a useful method to distinguish smokers from nonsmokers and is a marker for long-term nicotine intake, although an increased urinary cotinine concentration can be observed in people exposed to secondhand smoke (SHS). Because employer-based insurance is now affected by the use of tobacco, an understanding of the utility of nicotine and cotinine testing is important for employers. Although not commonly tested for, cotinine can also be used for screening adolescents who use these products or those who are exposed to SHS. Cotinine can be measured in serum, urine, saliva, and hair. Nonsmokers exposed to typical levels of SHS have serum cotinine concentrations less than 1 ng/mL. People with heavy exposure to SHS have serum cotinine concentrations in the range of 1 to 10 ng/mL, whereas active smokers almost always have serum cotinine concentrations higher than 10 ng/mL and occasionally higher than 500 ng/mL.[36]

PHARMACOGENETICS OF NICOTINE

The variation in nicotine response can be understood to be the result of the interaction between drug metabolism and drug receptor genotypes.[37] This variation in response is still an area of active investigation, and new data are adding to our understanding.

Drug Metabolism

Genetic variation in the *CYP2A6* gene can increase or decrease this enzyme's activity through altering the protein's expression level or its structure and function and thus nicotine metabolism. Multiple alleles of the *CYP2A6* enzyme have been identified (www.cypalleles.ki.se/cyp2a6.htm), including single nucleotide polymorphisms, duplications, deletions, and conversions, which have allowed for grouping people into slow, intermediate, and normal metabolizers.[38] People who carry reduced or null activity *CYP2A6* alleles are more likely to be nonsmokers or smoke fewer cigarettes per day, are less likely to progress to nicotine dependence, and may have an easier time quitting smoking and have a lower risk of lung cancer.[39] The opposite is the case for fast metabolizers.

Drug Receptor Genotypes

Each of the nAChRs is encoded for by a single *CHRN* gene. Large genomewide association study meta-analyses have brought to light the variations in the nAChR subunit genes that make the strongest genetic contribution to smoking-related habits.[40] The gene locus on chromosome 15q25.1 contains a dense set of highly correlated single nucleotide polymorphisms, in the *CHRNA5-CHRNA3-CHRNB4* gene cluster.[41] These may influence the age of initiation, the amount smoked, the development of nicotine dependence, and adverse effects such as lung cancer and chronic obstructive pulmonary disease. These associations appear to be more important in early-onset smokers, suggesting an age-associated relationship. In addition to smoking quantity and nicotine dependence, variants in nAChR genes have also been associated with alcohol and other substance dependencies as well as with a predisposition to schizophrenia.[41,42]

NICOTINE METABOLISM AND RACE, SEX, AND AGE

The rate of nicotine metabolism has been found to vary by sex and race, which may influence susceptibility to addiction and ability to quit. Differences in the *CYP2A6* allele frequencies may underlie this variability across sexes and ethnic groups. Up to 90% of white smokers are fast metabolizers. Latino smokers have rates of metabolism similar to white smokers. African-American smokers are more likely to be slow metabolizers, and Asian smokers have the slowest nicotine metabolic rates.[36] On average, slow metabolizers smoke fewer cigarettes than fast metabolizers and have higher quit rates, and the slower nicotine metabolism may account for their lower risk of nicotine addiction in studies in African-American smokers.[43]

Women metabolize nicotine faster than men, which may explain why women have more difficulty in quitting.[44] It is important to use caution in the clinical application of these data to individual patients because of heterogeneity and thus limitations of how racial categories are defined in the literature and the unique diversity of use and addiction trajectories of each patient. It is anticipated that further research will make individual-level assessments available in the future. Another factor affecting nicotine metabolism is the use of hormonal contraception. Studies indicate that these medications may accelerate cotinine metabolism in women, probably by an estrogen induction of *CYP2A6* that is independent of ethnicity and cigarette consumption.[45]

In the adolescent years, recent studies have confirmed differences in metabolic rate by race but not by sex.[46] However, the use of oral contraceptive pills, as in women, has been found to accelerate nicotine metabolism in adolescent tobacco-dependent smokers.[47] Another study by the same authors assessed the rate of nicotine metabolism in adolescents by using the nicotine metabolic rate as a reflection of the rate of clearance of nicotine. Slow metabolizers, because they have nicotine present for a longer time, are expected to smoke less. However, the findings were the opposite among slower metabolizers. They smoked more cigarettes per day and had higher addiction scores. These authors hypothesized that the brains of these slower metabolizers are exposed to greater amounts of nicotine for a longer period of time, and therefore, slower metabolizers may be more likely to develop addiction in early stages of smoking.[48]

HEALTH CONSEQUENCES OF EXPOSURE TO NICOTINE

Although there are adverse health effects attributable to nicotine, most of the adverse health consequences of tobacco use are the result of damage caused by tar, carbon monoxide, oxidizing chemicals, and other constituents in the product rather than nicotine.[14] Although smoking affects almost every system in the body, only some effects have been found to be directly related to nicotine use.

The data are insufficient to conclude that nicotine causes cancer, but there is evidence that it may increase the risk of oral, esophageal, and pancreatic cancer. In women, the intensity of current smoking has been noted to be an independent risk factor for high-grade cervical intraepithelial neoplasia, after controlling for cervical human papillomavirus infection.[49]

As noted previously, nicotine stimulates the release of various neurotransmitters in the CNS. Nicotine users endorse a reduction in pain, anxiety, and other negative emotional symptoms along with positive feelings of a mild euphoria, alertness, increased memory, and learning. Nicotine also has many neuroendocrine responses.[50] Although smokers say they smoke to control stress, studies show a significant increase in cortisol concentrations in daily smokers compared with occasional smokers or nonsmokers.[51] These findings suggest that, despite the subjective effects, smoking may actually worsen the negative emotional states. The effects of nicotine on the sleep-wake cycle through nicotine receptors may have a functional significance. Nicotine receptor stimulation promotes wake time and reduces both total sleep time and rapid eye movement sleep. Dopamine release in the CNS inhibits prolactin secretion from the anterior pituitary. However, decreased concentrations are only seen with long-term use, possibly because of desensitization of the nAChRs. Acute nicotine use increases prolactin secretion.

The cardiovascular effects of nicotine are mainly the result of stimulation of the sympathetic nervous system. In humans, nicotine has a biphasic physiologic response. In low concentrations, it acts as a stimulant by increasing adrenal catecholamines, but high doses of nicotine have the opposite effect, with hypotension and slowing of the heart rate.[52] nAChRs are found not only in neuronal and muscle cells but also in endothelial and immune cells. Nicotine induces proliferation of vascular smooth muscle cells and the migration of cells into blood vessels. Nicotine also increases lipolysis, resulting in the release of free fatty acids; over time, these effects cause an acceleration of coronary and peripheral vascular disease as well as an increase in the risk of strokes.

A relationship has been found between nicotine and inflammatory bowel disease. Although smoking has a deleterious effect on those with Crohn disease, it protects those with ulcerative colitis.[53,54] The risk of developing ulcerative colitis is lower in smokers (odds ratio: 0.41; 95% confidence interval:, 0.34–0.48). People who stop smoking and then resume smoking experience clinical improvement.[54] Many possible explanations have been proposed; these include the effects of smoking on cellular and humoral immunity, cytokines, eicosanoid-mediated inflammation, antioxidant and oxygen free radicals, endogenous glucocorticoids, colonic mucus, mucosal blood flow, thrombosis, gut permeability, and motility.[55] Recent research on microbiota changes with smoking may also help explain the influence of smoking on inflammatory bowel disease. Additional research on whether other chemicals in cigarettes may also be involved in this process is underway. However, no advantages over standard therapy have been advanced, and adverse effects of nicotine preclude a therapeutic recommendation.

Recent studies indicate that the parasympathetic nervous system controls innate immune responses through the modulation of the production of multiple inflammatory cytokines. Acetylcholine, as the principal neurotransmitter for the parasympathetic nervous system, has been shown to have antiinflammatory effects mediated through the nicotinic receptors on macrophages, inhibiting the proinflammatory cytokines from these macrophages.[56] The finding of distinct nAChR subtypes expressed on immune cells now suggests that this regulation is based on receptor affinity; evidence has been found for a crucial role for an α7 nAChR subtype in this process.

Clinical and experimental evidence indicates that nicotine is at least partly responsible for the progression of chronic kidney disease in cigarette smokers.[57] Nicotine also exacerbates acute kidney injury by various mechanisms.[58]

The bone marrow is innervated by cholinergic nerve fibers and macrophages, and other cytokine-producing cells express the α7 receptor and are functionally responsive to nicotine, which indicates a probable mechanism for control of inflammation. Similarly, microglial cells represent the largest class of phagocytes in the CNS and are regulated by acetylcholine. The activation of these microglia can be neurotoxic or neuroprotective and thus are important in CNS pathology. Several nicotinic agonists specifically targeting the α7 nAChR have been developed and are being studied for the treatment of neurologic, inflammatory, and infectious diseases. Long-term exposure to nicotine increases the risk of osteoporosis and bone fractures by creating an imbalance in bone remodeling through nicotine's effects on osteoclasts and osteoblasts.[59]

Nicotine also has an effect on body weight through mechanisms that are complex and not completely understood. The acute response is suppression of appetite and an increase in the metabolic rate, but chronic administration activates systems that increase appetite and decrease metabolic rate.[60] Many chronic smokers are overweight and have the metabolic syndrome with increased visceral adiposity. However, the reduction in appetite and the weight control are important effects that are more likely to appeal to younger females than males.[61] The increased appetite and weight gain that occur after stopping smoking can serve as a deterrent to smoking cessation for women.[62] Women who stop are also at greater risk of relapse to avoid the weight gain. Adequate pharmacotherapy of tobacco dependence may decrease or eliminate the weight gain associated with stopping. One study found that soon after abstinence from tobacco smoking, an increase in the plasma concentration of the appetite-stimulating peptide acetylated ghrelin occurs.[63] This finding could explain the increased food craving during nicotine withdrawal and subsequent weight gain.

Nicotine has a negative dose-related impact on both male and female fertility. In men, nicotine affects both gametogenesis and steroidogenesis. Nicotine also impairs nitric oxide synthesis, leading to erectile dysfunction. Although cigarette smoking has been associated with decreased fertility rates, adverse pregnancy outcomes, and higher risk of in vitro fertilization failure, the precise role of nicotine is still being evaluated both for the woman and for the fetus. The short-term safety of nicotine replacement therapy during pregnancy has been evaluated in a limited number of studies, but long-term effects on the fetus warrant further studies. Animal studies suggest that there may be an increased incidence of obesity, hypertension, type 2 diabetes, respiratory dysfunction, neurobehavioral effects, and impaired fertility.[64]

Two key studies have documented the developmental effects on offspring of women who smoked cigarettes prenatally and support concerns that tobacco or nicotine can have significant effects on early neurodevelopment in humans.[65,66] These studies have found that infants born to mothers who smoked during their pregnancies had reduced weight, length, and head circumference but also showed significant impairments in cognitive functioning, impulsivity, hyperactivity, and increased risk of developing an addiction disorder. These effects were seen throughout early childhood and persisted through adolescence and into young adulthood.

The neurobiological systems that are related to these behavioral problems are found in the dopamine, opioid neuropeptide, and cannabinoid systems in the amygdala and striatal regions of the brain and are important for the regulation of processes relevant to the behaviors noted previously.[67] Numerous studies that used animal models have identified the effects of both cigarette smoke or nicotine on brain development during fetal development, such as altered expression of nicotinic acetylcholine receptors in critical brainstem areas involved in autonomic function and altered excitability of neurons in brainstem areas involved in sensory integration.[68,69] Functional correlates of nicotine exposure include hypoventilation and apnea, as well as blunted chemoreflexes in response to hypoxia.[70–72]

Studies in human fetal subjects who have been exposed to nicotine have provided a better understanding of the molecular mechanisms underlying the developmental behaviors seen with prenatal nicotine exposure. For example, researchers have found that prenatal cigarette

exposure is associated with a decrease in the expression of the genes related to the endogenous opioid system in areas of the brain, the nucleus accumbens, that have been implicated in behavior motivation and mood regulation.[73] Prenatal tobacco exposure also alters both nicotinic and muscarinic receptors of the cholinergic systems in the brainstem and cerebellar regions.[67] Nicotinic acetylcholine receptors are strongly associated with serotonergic (5-HT receptors) in the brainstem during fetal development, and abnormalities of serotonergic neurotransmission in the brainstem have been consistent with neuropathologic findings in cases of sudden unexpected and unexplained death in infancy.[74,75] In first-trimester human fetuses, abnormal nicotinic receptor subunit levels have also been detected in the brainstem regions associated with sudden infant death syndrome.[76] Dysfunction of these brainstem regions, which can be associated with sudden infant death syndrome, is strongly associated with maternal cigarette use during pregnancy, and the alterations that are seen with gene expression in these cholinergic receptor subunits may be a contributing factor to the brainstem abnormalities seen in these infants.[77] These molecular alterations in gene expression as a result of prenatal nicotine exposure may be explained by epigenetic mechanisms, which is currently an area of active research.[67] The reader is referred to the American Academy of Pediatrics' technical report "SIDS and Other Sleep-Related Infant Deaths: Evidence Base for 2016 Updated Recommendations for a Safe Infant Sleeping Environment" for a comprehensive review on this subject.[78]

ACUTE TOXICITY

Children can ingest nicotine from the tobacco in cigarettes, chewing tobacco, pipe tobacco, nicotine gum and patches, and some insecticides. Most such incidents occur in children younger than 6 years, and the frequency and severity of outcomes are generally benign because of the ensuing emesis.[79,80] Recently, the newer electronic nicotine delivery systems with refillable cartridges that contain liquid nicotine have become a source of accidental exposure to a concentrated nicotine solution. The Centers for Disease Control and Prevention has reported a marked increase in e-cigarette liquid-related calls to poison control centers, from 1 per month (September 2010) to 215 per month (February 2014). More than half (51.1%) of calls involved children younger than 5 years.[81] A death of a child who ingested the concentrated nicotine solution used with electronic nicotine delivery systems was reported recently.[82]

Early symptoms of nicotine ingestion include a burning sensation in the mouth and throat, nausea, vomiting, confusion, dizziness, weakness, and drooling from increased salivation. Signs include tachycardia, tachypnea, hypertension, and agitation followed by bradycardia, hypotension, and respiratory depression. Severe poisoning leads to arrhythmias, coma, convulsions, and cardiac arrest. Skin or eye contact with concentrated liquid may cause irritation followed by variable absorption. Systemic signs or symptoms may follow. The lethal dose of nicotine has been estimated to be as little as 50 to 60 mg in adults, although this number is disputed. The lethal dose in children is probably much lower, between 1 and 13 mg/kg, and severe toxic reactions have been reported in children with doses as low as 2 mg. Nicotine liquid refills are available in various strengths ranging from 6 (0.6%) to 36 (3.6%) mg/mL. Assuming there are 20 drops in 1 mL of solution, 1 drop of 3.6% nicotine liquid will contain 1.8 mg nicotine. The dose of nicotine that has been estimated to be lethal for 50% of adults is between 0.8 and 13.0 mg/kg.[83] It has been estimated that 1 teaspoon (5 mL) of a 1.8% nicotine solution could be lethal to a 90-kg person.[84] The ingestion of a few drops of concentrated solution is enough to cause severe symptoms in young children.[85] For example, the ingestion of 1 to 2 drops of a 3.6% solution (1.8–3.6 mg) will put most children younger than 5 years in this category. With the use of a midrange of this lethal dose (6 mg/kg), the ingestion of 0.5 teaspoon (or 2 mL) of a concentrated nicotine solution could even be lethal to an average 12-kg, 20-month-old child.[4] Thus, children who have ingested ≥0.2 mg/kg of nicotine would be expected to be symptomatic and will need medical assessment. The refill liquids also contain unknown concentrations of oil of wintergreen (methyl salicylate), glycerin, and propylene glycol, which could also cause multiple toxidromes, including salicylism and cholinergic crisis.[86] The risk posed by nicotine liquid to children is an important anticipatory guidance topic to discuss with parents and caregivers. Preventive measures to reduce toxic ingestions include public education and legislation to improve the safety profile of electronic nicotine delivery system containers through limited volumes in available containers and child-proof packaging.

CESSATION

Although nearly half of adult smokers attempt to stop each year, <5% succeed because of nicotine's highly addictive nature.[14] Youth also attempt to quit, and those with greater evidence of dependence are more likely to have difficulty stopping. They make more quit attempts before being successful compared with adults. Approximately 4% of adolescent

smokers 12 to 19 years of age successfully quit smoking each year.[87] Starting smoking at a younger age is associated with more severe addiction and decreased rates of stopping smoking.[88]

Tobacco-dependence pharmacotherapy has been clearly shown to be safe and effective for adults and improves cessation rates. Current US Public Health Service guidelines recommend that all adults who smoke should be offered pharmacotherapy for tobacco-dependence treatment.[89] The current US Food and Drug Administration–approved tobacco-dependence treatment medications include the shorter-acting nicotine polacrilex gum (over the counter [OTC]), nicotine lozenge (OTC), nicotine nasal spray (by prescription), and nicotine oral inhaler (by prescription). These shorter-acting medications can be considered as "relievers," although their onset of action is much longer than that of cigarettes. Long-acting medications include the nicotine patch (OTC), bupropion (by prescription), and varenicline (by prescription). These can be considered as controller medications. Current approaches to tobacco-dependence pharmacotherapy initiate medications on the basis of severity of addiction and, on follow–up, adjusts medications depending on control of nicotine withdrawal.[90]

As discussed in the 2015 policy statement from the American Academy of Pediatrics, "Clinical Practice Policy to Protect Children From Tobacco, Nicotine, and Tobacco Smoke,"[91] pharmacotherapy can be considered to help moderately to severely tobacco-dependent adolescents who want to stop, despite challenges with adherence and the resulting high relapse rates. A possible concern for nicotine-replacement therapy use during adolescence, when smoking often begins, is that nicotine can change the neurodevelopmental trajectory. Further research is needed to evaluate the use of these medications in youth at various stages of use to better define the risks, benefits, and optimal treatment strategies and to inform optimal patient selection for the various pharmacotherapies.

E-cigarettes have been aggressively promoted as smoking cessation aids, but research studies have not been able to document their effectiveness in adults. Recent research suggests that the use of e-cigarettes may encourage, rather than discourage, the use of conventional cigarettes among US adolescents.[92,93]

A new approach to aid in tobacco cessation is the use of an antiaddiction vaccine that will induce antibodies that block the pharmacologic effects of nicotine.[94] Nicotine is nonimmunogenic and must be conjugated as a hapten to a protein carrier. The premise is that the antibody will attach to the nicotine molecule and prevent it from diffusing through the capillaries. It is then less likely to enter the brain and bind to the nAChRs. Although this approach has shown considerable promise in animal models, the research on its efficacy in humans thus far is limited. The serum nicotine-specific antibody titers induced by the vaccine vary greatly.[95] This variability means that a substantial number of nonresponders have low antibody titers that are not likely to be effective. Currently, the evidence does not show success with long-term smoking cessation with currently available vaccines.[96] Newer vaccines are now being designed to enhance the mean antibody titer and to reduce the number of nonresponders. There are no vaccines currently licensed for use in any country.

As noted previously, whereas nicotine is the key component of tobacco products required for the development and maintenance of addiction, behavioral, social, environmental, and psychological factors also contribute to this process. Most of the research on tobacco-dependence treatment of adolescents has focused on behaviorally based interventions. These interventions are most effective for those with mild degrees of nicotine dependence and least effective (although still of some benefit) for those with severe dependence.[97] Data are limited to support any 1 clinical approach to adolescent cessation of nicotine use. Effective behaviorally based strategies have focused on problem-solving skills and on providing support and encouragement.[89] The US Public Health Service recommends the following counseling modalities[98]: cognitive-behavioral strategies (self-monitoring and coping skills), motivational strategies (techniques to clarify desire for change and reduce ambivalence toward change), and social influence strategies (addressing social influences that serve to promote or maintain smoking). Dependence treatment is not the focus of this technical report, and the reader is referred to the previously mentioned 2015 policy statement from the American Academy of Pediatrics.[91]

CONCLUSIONS

Nicotine is the chemical in tobacco products that has a major role in the development of dependence. The rapidly developing brains of children and adolescents are particularly susceptible to nicotine addiction. Given the difficulty adolescents have with stopping tobacco use, the need for the prevention of tobacco use initiation is high.

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ABBREVIATIONS

CNS: central nervous system
nAChR: nicotinic acetylcholine receptor
OTC: over the counter
SHS: secondhand smoke

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