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Tobacco: The Smoking Gun

Prepared for The Citizens' Commission to
Protect the Truth

A CASA* White Paper

October 2007

Funded by:
American Legacy Foundation

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Accompanying Statement by Joseph A. Califano, Jr., Chairman and President

Despite the fact that the dangers associated with tobacco use have been known for some time and scientific evidence confirming these dangers has grown dramatically over the past 40 years, public debate has continued about the implications of the risks of smoking for tobacco regulation.

The evidence now available, including new research on the damaging effects of nicotine on the adolescent brain and CASA's new analysis of the statistical connection between early initiation of smoking and increased likelihood of alcohol and other drug use and dependence, sounds an alarm for parents, healthcare providers, teachers and others responsible for the health and safety of our children and teens. Smoking by teens may well signal the fire of alcohol and other drug abuse and mental illnesses such as depression and anxiety disorders.

Teens who are current smokers are more than five times likelier to drink and 13 times likelier to use marijuana than nonsmokers. They are also nine times likelier to meet the medical criteria for past year alcohol abuse or dependence and 13 times likelier to meet the medical criteria for abuse and dependence on an illegal drug.

Compared to people who have never smoked, those who begin smoking by age twelve are:

- Sixteen times likelier to meet the medical criteria for marijuana abuse or dependence.
- Almost five times likelier to meet the medical criteria for alcohol abuse or dependence.
- More than three times likelier to binge drink.

- Almost seven times likelier to use other illegal drugs like cocaine and heroin.

Teens who start smoking early are more likely to report symptoms of mental illness such as hopelessness, depression and worthlessness. Smokers ages 12 to 17 are twice as likely as nonsmokers to suffer from symptoms of depression. This is of particular concern among girls and young women--they can be more susceptible both to nicotine's effects on the brain and mental illness, particularly depression.

Findings from animal studies and advanced brain imaging techniques suggest that nicotine is hazardous to the adolescent brain, affecting it differently than an adult brain and increasing a young person's vulnerability to the effects of smoking. The relationship between early smoking and later use of other addictive substances or mental illness may be the result of critical changes in the brain that can be caused by exposure to nicotine. These changes include:

- Increases in the number of the brain's receptors for nicotine associated with a greater risk of cigarette consumption, nicotine dependence and difficulty quitting smoking;
- Increased levels of dopamine in the brain which may make the reward associated with nicotine stronger and increasingly compulsive;
- Changes in serotonin levels receptors that are associated with depression; and
- Changes to brain receptors that are associated with an increased preference for other addictive drugs.

We have known for a long time that smoking causes deadly and crippling cancers and cardiovascular and respiratory diseases. Now the public health case against tobacco for hiking the chances of damaging our children's developing brains in ways

that can increase their risk of alcohol and other drug abuse and mental illness is clear. The time has come to curb cigarette advertisements and promotions by the nicotine pushers and step up campaigns like the American Legacy Foundation's **truth**® effort to protect our nation's children. Time for debate is long past and it is time to act.

To make this new research accessible to policymakers and the public, the *Citizens' Commission to Protect the Truth* asked CASA to prepare this White Paper, *Tobacco: The Smoking Gun*. CASA is issuing this paper as an alert to parents, healthcare professionals, teachers and others responsible for young people to prevent youth smoking; intervene to stop it; and be aware that such use also may signal mental illness and alcohol and other drug use that require intervention and possibly treatment.

This White Paper makes recommendations for a broad range of policy changes as well. Scientific evidence now supports the conclusion that all forms of tobacco product advertising, marketing and promotion should be sharply restricted, the U.S. Food and Drug Administration should have comprehensive authority to regulate tobacco products, and evidence-based efforts such as the **truth**® counter-advertising campaign, other counter-advertising initiatives, and prevention and cessation programs must be funded adequately.

Many individuals made important contributions to this work. We extend special thanks to Cheryl Heaton, DrPH and the American Legacy Foundation for their support of this project.

For donating their time and expertise in reviewing a draft of this paper, we thank Ruben Baler, PhD of the National Institute on Drug Abuse's Office of Science Policy and Communications; Timothy P. Condon, PhD, Deputy Director of NIDA; Matthew C. Farrelly, PhD, senior economist and director, Public Health Economics and Policy Research Program, Research Triangle

Institute; Cheryl Heaton, DrPH, President and Chief Executive Officer of the American Legacy Foundation; Alan I. Leshner, PhD, Chief Executive Officer and Executive Publisher, Science, of the American Association for the Advancement of Science; Lucinda L. Miner, PhD, Deputy Director of NIDA's Office of Science Policy and Communications; Julius B. Richmond, MD, John D. MacArthur Professor of Health Policy Emeritus, Department of Social Medicine, Harvard Medical School; and Theodore Slotkin, PhD, Professor, Department of Pharmacology & Cancer Biology and Director of Graduate Studies, Integrated Toxicology & Environmental Health Program, Duke University.

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While many individuals and institutions contributed to this effort, the findings and opinions expressed herein are the sole responsibility of CASA.

Tobacco: The Smoking Gun

Despite more than 40 years of research, advocacy and policy change, every day approximately 4,000 young Americans light up for the first time.¹

While negative effects of tobacco use have been known for some time,^{* 2} more recent research demonstrates that tobacco use at a young age can set children and adolescents down a path of lifelong nicotine addiction, chronic illness and premature death.³

An emerging body of work points to additional harms of smoking among youth. The nicotine in tobacco products can produce structural and chemical changes in the developing brain that make young people vulnerable to future alcohol and other drug addiction and mental illness.⁴ This latest research, added to the already established list of health consequences of nicotine use, further discredits any lingering doubts about the serious harm of early tobacco use.

Adolescence is a period of dramatic psychological and physical change as children move into young adulthood. Advances in medicine and technology have enriched our understanding of this critical period of development, revealing that the adolescent brain itself is a work in progress. In addition to the hormonal changes typically associated with teen behavior, the immature brain helps to account for common teenage characteristics such as risk taking and moodiness.⁵ The structural and chemical transformations that occur from early adolescence into the early 20s are critical to the progression to adulthood, but the fact that the teenage brain is so malleable may confer substantial vulnerability to substance abuse and mental health problems.⁶

While there are multiple pathways to substance use and mental illness, especially in young people, animal research establishes a strong correlation between early nicotine exposure and subsequent use of alcohol, marijuana, cocaine and heroin. This research also provides a possible biological

* The first known documentation of tobacco's damaging health effects was published anonymously in 1602.

explanation for the theory that the use of tobacco products can increase the chances of later alcohol and other drug use.^{* 7} By raising the number of nicotinic receptors in the brain, nicotine alters the brain's response to addictive substances like alcohol and increases the risk of alcohol use;⁸ nicotine also increases the brain chemical associated with alcohol and other addictive substances--dopamine--that produces a sense of reward or reinforcement.^{† 9} Nicotine interacts with the marijuana-like receptors[‡] in the brain to alter naturally occurring brain chemicals which may increase vulnerability to marijuana use and dependence.¹⁰ Adolescent rats exposed to nicotine show a preference for cocaine, which appears to be linked to the effects of nicotine on dopamine.^{§ 11} And, nicotine alters opioid receptors^{**} and other brain chemicals associated with heroin^{††} that may increase the risk of subsequent heroin use.¹²

Animal studies have shown that early nicotine exposure also may increase the risk of developing mood disorders, anxiety disorders and other mental illnesses. Nicotine exposure reduces the function of the brain chemical serotonin, which has been associated with depression.¹³ Animal studies show that adolescents exposed to nicotine exhibit behaviors suggestive of anxiety or panic.¹⁴ Preliminary research also suggests that early exposure to nicotine can cause chemical changes

* According to the "gateway theory" of substance use, the use of certain substances, like nicotine or alcohol, may increase the risk of using other substances, like marijuana and other illicit drugs. This theory is considered controversial by researchers who believe that, despite the evident link between early smoking or drinking and later use of other substances of abuse, it oversimplifies a highly complex process with multiple genetic, behavioral and environmental determinants.

† The higher dopamine levels make the brain much more sensitive to chemicals found in substances of abuse that further increase dopamine; this hyper-reactive state is associated with physiological cravings for substances of abuse such as alcohol and illicit drugs.

‡ Cannabinoid receptors.

§ Nicotine increases the density of dopamine transporters.

** μ -opioid receptors.

†† met-enkephalin.

in the brain associated with other mental illnesses such as post-traumatic stress disorder.¹⁵

Why Do Teens Use Tobacco Products?

In 2005, 3.4 million 12- to 17-year olds (13.2 percent) reported using a tobacco product in the past month and 2.7 million such teens (10.8 percent) reported smoking cigarettes.¹⁶ However delivered--through the use of cigarettes, cigars and chewing or smokeless tobacco--nicotine, like other substances of abuse, increases the level of the brain chemical dopamine that affects the reward and pleasure pathways in the brain. Immediately after exposure, nicotine has a stimulating effect on the body, causing a sudden release of glucose, and raising blood pressure, heart rate and breathing. The stimulating effects of nicotine belie the perceived calming effects some smokers experience from tobacco use. The relaxing sensation resulting from smoking actually appears to stem from a reduction in withdrawal symptoms that begin to occur between smoking episodes.¹⁷

In addition to these physiological effects, teens report smoking cigarettes to enhance their image, be rebellious, fit in or appear mature or cool. Other common teen expectations that perpetuate smoking include the belief that smoking will help control weight, improve a depressed mood and help cope with stress.¹⁸ Environmental factors--such as parents or peers who smoke, exposure to glamorous media images of smoking and exposure to tobacco industry advertising--also increase the risk of teen smoking.¹⁹

The Adolescent Brain

While the size of the human brain does not change dramatically after age six, adolescence marks a period of significant brain modification and refinement. Between the ages of six and 12, the nerve cells (neurons) in the brain multiply and develop new pathways for nerve signals to travel. During this time, there is a proliferation gray matter in the brain--nerve cells that are responsible for thinking and other forms of information processing. This period soon is followed by a "pruning" phase that continues into the early 20s where the amount of gray matter in the brain

declines. At the same time, the brain's white matter--fatty material covering parts of the nerve cell that makes transmission of nerve signals faster and more efficient--becomes thicker.²⁰ The parts of the brain responsible for sensory and spatial functions* are the first to mature fully. The part of the brain responsible for higher-level functions like decision-making, impulse control, learning and memory† is the last region of the brain to develop fully.²¹

The lack of fully-developed decision making and impulse control skills combined with the hormone changes of puberty compromise a teen's ability to assess risks and make them uniquely vulnerable to substance abuse.²² The sex hormones responsible for the physical changes of puberty are particularly active in the part of the brain that controls emotion, pleasure and memory formation.‡

The surge in the female hormone estrogen and the male hormone testosterone during puberty is associated with the risk taking and sensation seeking that often characterize teenage behavior. At the same time, the parts of the brain that help weigh consequences, understand and accept responsibility and exercise judgment are still under construction during the teen years.²³ Each of these developments alone can contribute to a teen's tendency to engage in substance use but together they compound the potential for risk.

Nicotine: Hazardous to the Adolescent Brain

Structural and chemical changes that can result from nicotine exposure have immediate and long-term implications for health and behavior. When nicotine activates its receptors on the surface of nerve cells, numerous hormones and brain chemicals--neurotransmitters--are released which produce changes in the brain and throughout the body.²⁴

* The occipital and parietal lobes of the brain, located toward the back of the head.

† The prefrontal cortex, located toward the front of the head.

‡ The limbic system.

To better understand these brain and behavioral changes, animal models are widely used in biological research, particularly when such research on humans is unethical or impossible. Findings from animal studies that include early nicotine exposure commonly are considered suggestive of human biology and behavior.

Animal studies and advanced brain imaging techniques have revealed that nicotine is hazardous to the adolescent brain,[§] affecting it differently than an adult brain and increasing a young person's vulnerability to the effects of smoking. Animal research has found that nicotine produces greater brain cell loss and damage²⁵, longer-lasting neurochemical alterations--including increased density of brain cell receptors that bind with nicotine**²⁶--and greater sensitivity to the rewarding effects of nicotine in adolescents relative to adults.^{†† 27}

Greater brain cell loss and damage. Although the total number of brain cells typically does not change following the proliferation of neurons that occurs soon after birth, the brains of adolescent rats show substantial cell damage and cell loss as a result of nicotine exposure.²⁸ The mechanisms of cell damage and loss that result from tobacco exposure are twofold: nicotine directly inhibits the proliferation of neurons and causes actual cell disintegration.²⁹ Cell damage and loss occur even at very low levels of nicotine exposure; these changes to the maturing brain affect the way brain cells transmit messages and ultimately can lead to abnormal physiological performance such as altered cardiac function.³⁰

Greater effects on key brain chemicals. Smoking cigarettes causes many changes in the neurochemistry of the adolescent brain; in particular, nicotine causes changes in the levels of certain neurotransmitters, including dopamine, norepinephrine and serotonin, which are

§ While research shows that nicotine replacement therapy (NRT) can be beneficial in supporting smoking cessation, there is limited evidence on its effectiveness in adolescents.

** Nicotinic acetylcholine receptors or nAChRs.

†† These changes reflect the effect of nicotine on the brain's cholinergic system.

associated with alcohol and other drug abuse and other mental health disorders.

Nicotine exposure increases the amount of dopamine in the brain.³¹ The activity of this neurotransmitter, which is critical to the development of substance dependence, has a strong influence on reward-related learning in adolescence.³² The immaturity of critical brain regions contributes to impulsive behavior and a preference for high-risk, low-benefit situations during adolescence; when this developmental immaturity is coupled with cellular changes caused by repeated dopamine stimulation by nicotine, the reward associated with tobacco use becomes stronger and increasingly compulsive.³³ Animal studies have shown that the pathways affected by dopamine, particularly in the midbrain, become less sensitive to nicotine stimulation over the long-term, resulting in classic symptoms of dependence: tolerance and withdrawal symptoms if one stops using nicotine.³⁴

Nicotine also has been shown in animal research to influence levels of another neurotransmitter, norepinephrine, especially in females.³⁵ Norepinephrine acts on regions of the brain associated with attention and impulsiveness; abnormal levels of this important chemical in the brain are associated with disorders such as depression, attention-deficit-hyperactivity disorder and anxiety.³⁶ Research has found that nicotine affects norepinephrine levels in the hippocampus--a region of the brain associated with memory.³⁷

In the case of serotonin, rodent studies show that adolescent nicotine exposure increases serotonin receptor activity in key brain regions[†] that also are associated with drug abuse.³⁸ Adolescent nicotine exposure also causes changes in serotonin receptors that are associated with depression.³⁹

Greater sensitivity to nicotine. Compared to the typical adult smoker, adolescents are more likely to show an increase in the number of nicotinic

* Lower levels of norepinephrine are associated with attention-deficit/hyperactivity disorder and depression; higher levels of norepinephrine are associated with anxiety.

[†] Specifically the midbrain and brainstem.

receptors[‡] on nerve cells following exposure to nicotine and this increase occurs among adolescent rats at relatively lower levels of use.⁴⁰ An increase in nicotinic receptors is associated with a greater risk of cigarette consumption, nicotine dependence and difficulty quitting smoking, in part because higher nicotine receptor density provides more opportunities for nicotine and other brain chemicals associated with addiction--such as dopamine--to bind to their receptors and produce rewarding or reinforcing effects.⁴¹ Animal studies show that adolescents are less sensitive than adults to the inhibiting (activity-decreasing) effects of nicotine and more sensitive to nicotine's stimulating (activity-increasing) effects; one of the stimulating effects of nicotine that is stronger in adolescents than in adults is the increase in dopamine, the neurotransmitter linked to substance abuse, addiction⁴² and certain forms of mental illness.⁴³

Nicotine and Alcohol Use

Adolescent smoking is highly correlated with alcohol use, abuse and dependence.⁴⁴ In 2005, 16.5 percent of teens, ages 12 to 17, reported drinking alcohol in the past month.⁴⁵ Almost 40 percent of these current drinkers are current smokers.⁴⁶ Teens ages 12 to 17 who are current smokers are more than five times likelier than nonsmokers to be current drinkers (59.1 percent vs. 11.3 percent).⁴⁷

Support for the notion that smoking may increase the likelihood of drinking⁴⁸ comes from an examination of individuals who began smoking at a young age. CASA's analysis of data from the *National Survey on Drug Use and Health (NSDUH)*[§] indicates that individuals who initiated

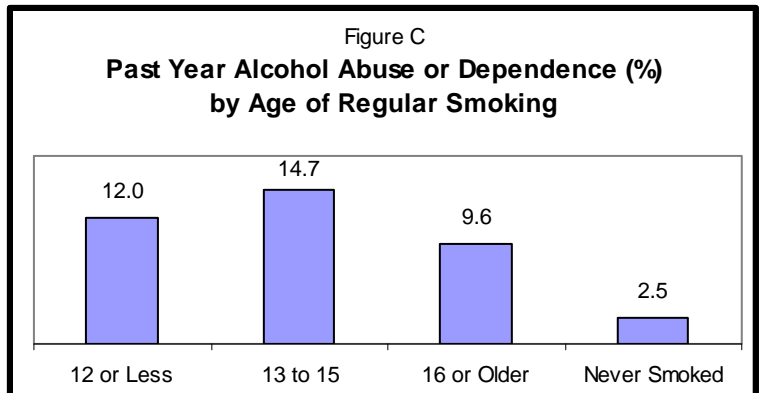
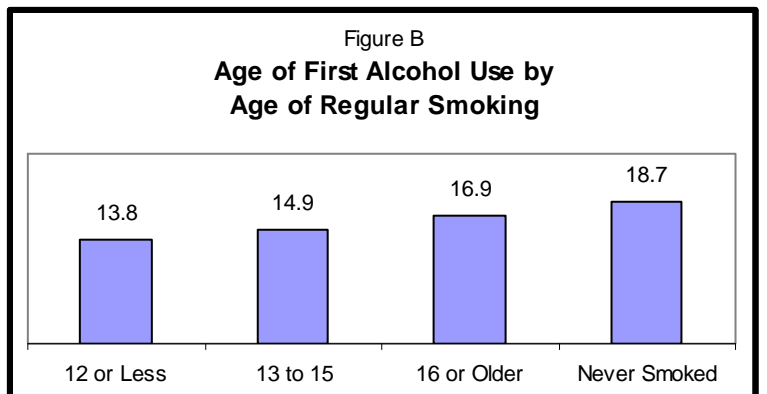
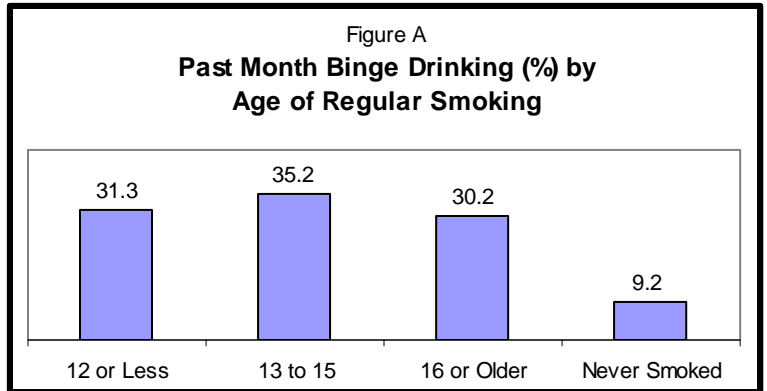
[‡] nAChRs.

[§] The *NSDUH* is a cross-sectional national survey of the noninstitutionalized population in the United States, ages 12 and older. It is known to underestimate considerably all forms of substance use in the U.S. Because it is administered in the home, respondents--particularly teens--tend to under-report their substance use. Moreover, the survey does not include high-risk institutionalized populations, such as prison inmates, hospital patients, nursing home residents, patients in drug abuse treatment and others who cannot be reached

smoking at a young age--12 or younger--are likelier to report current (past 30 day) alcohol use than those who never smoked (51.2 percent vs. 30.6 percent). Early smoking initiation also is associated with an increased risk of binge drinking.* For example, individuals who began smoking regularly at age 12 or younger are more than three times likelier to report binge drinking than those who never smoked (31.3 percent vs. 9.2 percent).⁴⁹ (Figure A)[†]

The earlier the initiation of smoking, the likelier an individual is to begin drinking at an early age. For example, the average age of alcohol initiation among those who began smoking regularly at age 12 or younger is 13.8; the average age of alcohol initiation among those who began smoking regularly at age 16 or older is 16.9; the average age among those who never smoked is 18.7.⁵⁰ (Figure B)

Early initiation of smoking also is linked to an increased risk of alcohol abuse and dependence. CASA's analysis of *NSDUH* data finds that individuals who initiated smoking regularly at age 12 or younger are 1.3 times likelier to meet diagnostic criteria for past year alcohol abuse or dependence than those who initiated regular smoking at age 16 or older (12.0 percent vs. 9.6 percent) and 4.8 times likelier to have an alcohol use disorder than individuals who report never smoking (12 percent vs. 2.5 percent).⁵¹ (Figure C)



in a home (e.g., the homeless). Despite these limitations, the *NSDUH* contains the best available data for this type of analysis.

* Consuming five or more drinks on one occasion.

† CASA's analysis of the 2005 *NSDUH* was conducted using five categories of smoking age; in addition to the four presented in the figures, the category "Never Regularly Smoked" was omitted for presentation clarity.

CASA's analysis of *NSDUH* data indicates that among teens of this age, current smokers are significantly likelier than nonsmokers to meet clinical diagnostic criteria* for past year alcohol abuse or dependence (27.5 percent vs. three percent).⁵² Likewise, teens who were dependent on nicotine† in the past 30 days are significantly likelier than other teens to meet diagnostic criteria for past year alcohol abuse or dependence (34.5 percent vs. 4.5 percent).⁵³ Other research finds that 19 percent of teen smokers drink heavily--consuming more than 50 drinks in one month--compared with less than one percent of teen nonsmokers.⁵⁴ Although a statistical analysis of this type cannot document a causal relationship, the more frequently teens and young adults smoke, the more likely they are to suffer from alcohol dependence as adults.⁵⁵

Explaining the Link

There are many factors that contribute to the relationship between tobacco and alcohol use. Twin studies, for example, show that genetics play a role in the initiation of smoking, whether a person will be a light, moderate or heavy smoker, and in the concurrent use of cigarettes and alcohol.⁵⁶ Environmental factors--such as parental attitudes and behavior, peer influence, school experience, neighborhood characteristics, cultural values, advertising and the media--also have been implicated in the link between smoking and drinking.⁵⁷ Neurobiological research in animals has demonstrated a distinct temporal link between nicotine exposure and alcohol consumption, with a clear progression from cigarette use to alcohol use.⁵⁸ While it is possible that the brains of some individuals might be predisposed to initiate smoking and alcohol use at an earlier age than others, these findings suggest that nicotine exposure at a young age may cause neurological changes that could increase teens' vulnerability to alcohol use and abuse.

* Based on the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV).

† As defined in the *NSDUH*, nicotine dependence is based on five factors, each comprised of several criteria: smoking drive, nicotine tolerance, continuous smoking, behavioral priority and patterns of smoking.

Nicotine and ethanol--the chemical compound that forms the alcohol content in beer, wine and liquor--share a number of pathways in the brain that contribute to the reinforcing and rewarding effects of these substances, such that exposure to one can increase the likelihood of future use or abuse of the other.⁵⁹ Like nicotine, ethanol activates regions of the brain involved in addiction‡ and increases the amount of dopamine in the brain. This process appears to involve the brain's nicotine receptors; animals exposed to ethanol in the presence of chemicals that block the brain's nicotine receptors§ demonstrate reduced levels of dopamine in the brain and a reduced likelihood of seeking alcohol.⁶⁰

Adolescent rats exposed to nicotine prior to ethanol demonstrate higher dopamine levels than adolescent rats exposed only to ethanol; the higher dopamine level significantly increases their preference for alcohol and thus the amount they consume.⁶¹ This finding may help explain why the earlier a person starts using cigarettes, the more likely he or she is to use alcohol and develop alcohol dependence later in life.⁶² Following chronic nicotine exposure, there is an increase in the number of nicotine receptors--also known as upregulation--especially in adolescents.⁶³ When nicotine exposure occurs prior to drinking, nicotine receptor upregulation provides more receptors for the ethanol to act upon; this process of upregulation increases the urge to consume alcohol.⁶⁴ The increase in the rewarding effects of ethanol in the presence of nicotine may help explain the relationship between nicotine exposure and increased risk of alcohol consumption.

Nicotine exposure also is a trigger for resuming alcohol consumption after a period of abstinence from either substance.⁶⁵ This occurs across a range of levels of nicotine exposure. Animal studies have shown that alcohol consumption remains elevated even after animals no longer receive nicotine.⁶⁶ Similar patterns of nicotine exposure and alcohol consumption have been documented in teens; even when adolescents quit smoking, their risk of developing a substance use

‡ The limbic system.

§ Specifically mecamylamine, a nicotinic antagonist that blocks nicotine from binding with its receptors.

disorder such as alcohol dependence does not necessarily decline.⁶⁷

Nicotine and Illicit Drug Use

Young people who use illicit drugs often also use tobacco. Almost 10 percent of youth ages 12 through 17 in the U.S. report current use of illicit drugs.⁶⁸ More than 46 percent of current illicit drug users are current smokers.⁶⁹ Teens ages 12 to 17 who are current smokers are more than 8.5 times likelier than nonsmokers to currently use illicit drugs (46.7 percent vs. 5.40 percent).⁷⁰ Cigarette smoking often precedes the use of drugs like marijuana, cocaine and heroin. The number of youth using other illicit drugs is too small to conduct reliable analyses on the link between smoking at a young age and the use of these drugs.⁷¹

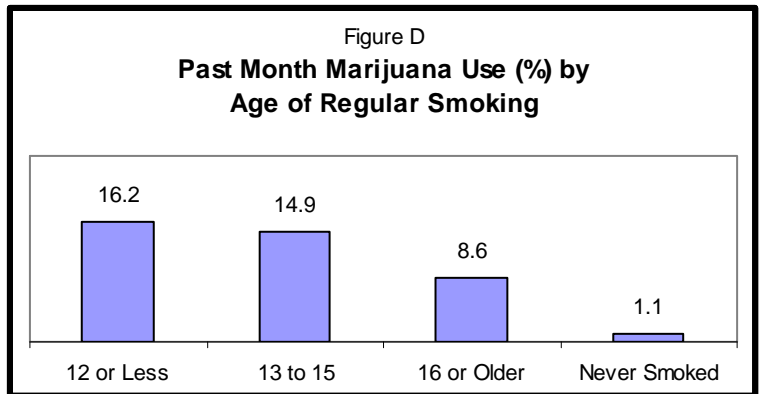
CASA's analysis of data from the *NSDUH* further indicates that among teens ages 12 to 17, current smokers are 13 times likelier than nonsmokers to meet diagnostic criteria for past year abuse or dependence on an illicit drug (25.8 percent vs. two percent).⁷² Likewise, teens who abused or were dependent on nicotine in the past 30 days are nearly 10 times likelier than other teens to meet diagnostic criteria for past year abuse or dependence on an illicit drug (33.2 percent vs. 3.4 percent).⁷³

Marijuana

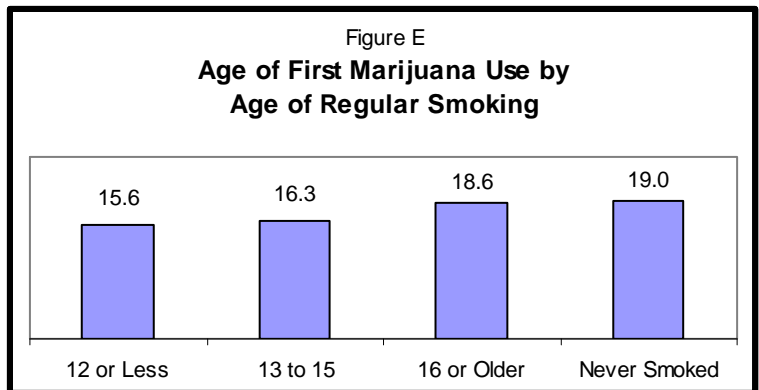
Marijuana is the most widely used illicit drug among teens--in 2005, 6.8 percent of teens ages 12 to 17 were current marijuana users⁷⁴--and cigarette smoking is linked to marijuana use in that age group. Of these, 63.9 percent are current smokers.⁷⁵ In this age group, current smokers are 13.4 times likelier to use marijuana than nonsmokers.⁷⁶ Compared with their nonsmoking peers, teens who smoke cigarettes use more marijuana and use it more frequently.⁷⁷ One study showed that youth who begin smoking cigarettes during middle school are nearly three times likelier than their nonsmoking peers to progress to marijuana use.⁷⁸ Nicotine dependence is associated with an increased risk of progression

from no marijuana use to repeated and regular use.⁷⁹

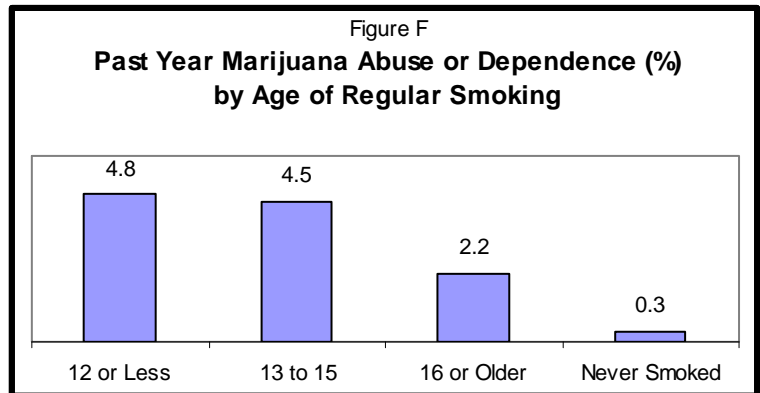
CASA's analysis of *NSDUH* data indicates that individuals who initiated smoking at a young age--12 or younger--are nearly twice as likely to report current marijuana use as those who initiated smoking at age 16 or older (16.2 percent vs. 8.6 percent) and nearly 15 times likelier to be marijuana users than individuals who never smoked (16.2 percent vs. 1.1 percent).⁸⁰ (Figure D)



The earlier the initiation of smoking, the likelier an individual is to begin using marijuana at an early age. For example, the average age of marijuana initiation among those who began smoking regularly at age 12 or younger is 15.6; the average age of marijuana initiation among those who began smoking regularly at age 16 or older is 18.6 years; the average age among those who never smoked is 19. (Figure E)



Early initiation of smoking is linked to an increased risk of marijuana abuse and dependence. CASA's analysis of *NSDUH* data finds that individuals who initiated smoking regularly at age 12 or younger are more than twice as likely to meet diagnostic criteria for past year marijuana abuse or dependence as those who initiated regular smoking at age 16 or older (4.8 percent vs. 2.2 percent) and 16 times likelier than individuals who report never smoking to meet diagnostic criteria for marijuana abuse or dependence (4.8 percent vs. 0.3 percent).⁸¹ (Figure F)



Explaining the link. Researchers long have debated the causal relationship between tobacco and marijuana use, as epidemiological studies have yielded complex and sometimes contradictory findings.⁸² More recent experimental animal research, however, has shown that nicotine exposure at a young age can elicit neurochemical and behavioral changes associated with an increased risk of subsequent marijuana use.⁸³

While marijuana and nicotine act on different types of receptors in the brain, their receptors are found in many of the same regions.^{* 84} This overlap may explain how changes in the brain that occur as a result of early nicotine exposure might influence future use of marijuana. For example, one study of adult rats found that exposure to nicotine causes significant decreases in endocannabinoid levels[†] in regions of the brain that are strongly affected by adolescent nicotine exposure.⁸⁵ Decreasing the level of these naturally-occurring chemicals may increase the vulnerability to substances like marijuana which imitate the actions of those chemicals.

Systems of the brain affected by marijuana and nicotine interact to influence how an individual responds to these substances.⁸⁶ For example, one

study demonstrated that exposure to a substance similar to marijuana[‡] did not induce any changes in anxiety; when this substance was administered following low levels of nicotine exposure, male rats showed an increase in anxiety-like behaviors.⁸⁷ This finding may reveal changes in the brain's receptors for marijuana that occur as a result of nicotine exposure.⁸⁸ A similar study conducted with human volunteers showed that nicotine exposure prior to marijuana use enhanced both the personal and physical effects of marijuana, such as feeling stimulated and altered heart rate; these effects were more pronounced among males.^{§ 89}

Other Illicit Drugs

Almost five percent of youth ages 12 through 17 in the U.S. report current use of an illicit drug other than marijuana.⁹⁰ Nearly 45 percent of these teens are current smokers.⁹¹ Teens ages 12 to 17 who are current smokers are 6.7 times likelier than nonsmokers to currently use an illicit drug other than marijuana (20.1 percent vs. 3.0 percent).⁹²

CASA's analysis of data from the *NSDUH* finds that individuals who initiated smoking at age 12 or younger are 2.5 times as likely to report current use of an illicit drug other than marijuana as those who initiated smoking at age 16 or older (11.2

* Cannabinoid and nicotinic receptors are found, for example, both in the hippocampus and amygdala.

† Endocannabinoids are chemicals produced by the body that act on cannabinoid (chemical compounds that are the active principles of marijuana) receptors; changes in endocannabinoid levels were found specifically in the brainstem, hippocampus, striatum and cerebral cortex.

‡ This study examined the effects of CP 55,940, a cannabinoid receptor agonist which binds to the same receptors as marijuana.

§ The observed gender differences in these studies have been attributed to a number of factors, including hormonal differences or different patterns in the development of the brain's receptors for marijuana.

percent vs. 4.5 percent) and seven times likelier than individuals who never smoked to report current use of an illicit drug other than marijuana (11.2 percent vs. 1.6 percent).⁹³ (Figure G)

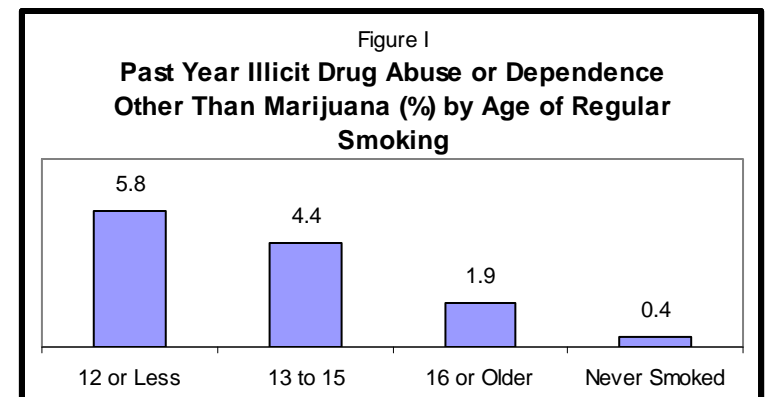
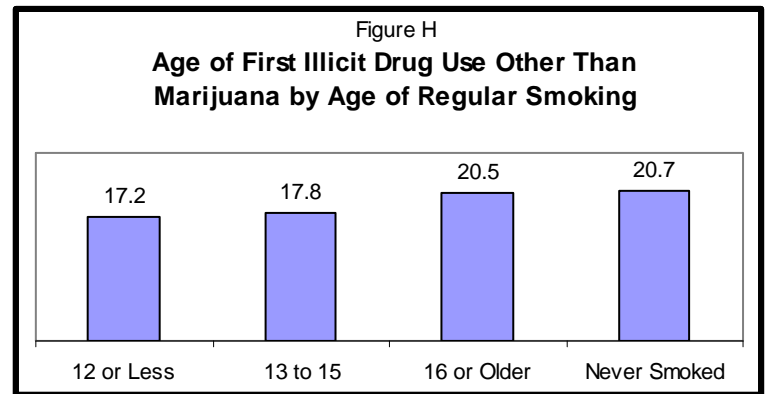
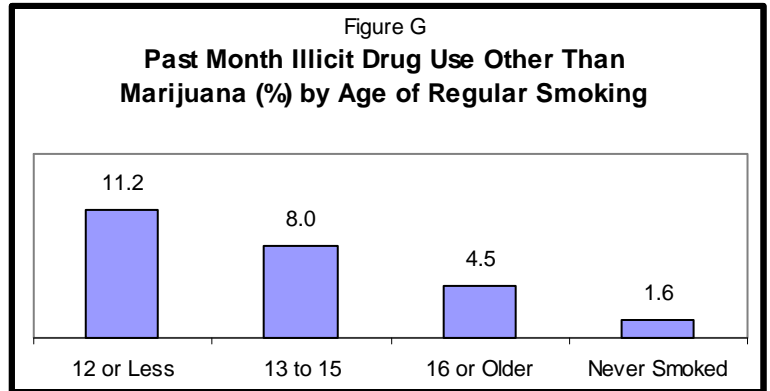
Likewise, the earlier the initiation of smoking, the likelier an individual is to begin using illicit drugs other than marijuana at an early age. For example, the average age of first use of an illicit drug other than marijuana among those who began smoking regularly at age 12 or younger is 17.2; the average age of illicit drug use initiation among those who began smoking regularly at age 16 or older is 20.5; the average age among those who never smoked is 20.7.⁹⁴ (Figure H)

Individuals who initiated smoking regularly at age 12 or younger are three times likelier to meet clinical diagnostic criteria for past year abuse or dependence on an illicit drug other than marijuana than those who initiated regular smoking at age 16 or older (5.8 percent vs. 1.9 percent) and 14.5 times likelier than individuals who report never smoking to meet diagnostic criteria for abuse or dependence on an illicit drug other than marijuana (5.8 percent vs. 0.4 percent).⁹⁵ (Figure I)

Cocaine.* Compared with other drugs of abuse, the rate of cocaine use is relatively low among adolescents; in 2005, less than one percent of youth ages 12 through 17 reported being current cocaine users.⁹⁶ Findings from animal studies suggest that adolescents who smoke cigarettes may be at greater risk for subsequent cocaine use; early exposure to nicotine has been shown to change the way the brain responds to cocaine.⁹⁷

Like nicotine, the pleasurable effects of cocaine use are, at least in part, the result of increases in the level of dopamine in the brain. One study showed how adolescent rats exposed to nicotine are more sensitive to cocaine than rats who are not exposed to nicotine. Adolescent rats who received nicotine prior to cocaine exposure were significantly more physically active than their

* An analysis of the likelihood of cocaine use among smokers versus nonsmokers is unavailable due to small sample size.



counterparts who did not receive any nicotine.^{† 98} When the experiment was replicated with adult rats, the effects of cocaine exposure on physical activity were significantly weaker than that which was observed among the adolescent rats.⁹⁹ The link between nicotine and increased cocaine sensitivity is found even at low levels of nicotine exposure; a study of male mice showed that chronic administration of small amounts of nicotine during adolescence caused more movement following adult cocaine exposure as

† Among the nicotine-exposed rats, males were more sensitive than females to cocaine's stimulatory effects.

compared with mice who did not receive any nicotine during adolescence.¹⁰⁰ Other animal research demonstrates that nicotine exposure can increase the preference for cocaine.¹⁰¹ One experiment injected nicotine- versus saline-exposed rats with cocaine and found that those exposed to nicotine prior to cocaine demonstrated an increased preference for cocaine relative to those exposed first to saline.¹⁰² These animal studies suggest that smoking at a young age may increase vulnerability to cocaine use.¹⁰³

Heroin.* In 2005, 0.1 percent of youth ages 12 through 17 reported current use of heroin.¹⁰⁴ Yet heroin use is associated with cigarette smoking.¹⁰⁵ One study of adolescents admitted for heroin dependence treatment found that 92 percent also smoked cigarettes.¹⁰⁶ Some research suggests that the high prevalence of tobacco use among heroin users relative to the general population may be due to changes to opioid receptors that occur as a result of nicotine exposure.

While nicotine and heroin elicit their effects through different neurotransmitter systems in the brain, nicotine exposure leads to changes in opioid receptors[†] and other brain chemicals associated with heroin use.[‡] In one study of rats, nicotine exposure increased the number of opioid receptors, which is linked to greater vulnerability to heroin use and dependence.¹⁰⁷ Other animal research supports the notion that high levels of nicotine exposure during adolescence may increase the risk of using opioids like heroin, particularly in males.¹⁰⁸

Other drugs of abuse. Animal research indicates that nicotine exposure causes changes in the brain that may increase its susceptibility to the use of and dependence on the benzodiazepine diazepam (Valium). Chronic exposure of rats to nicotine increases the concentration of benzodiazepine receptors¹⁰⁹; similar effects in humans could lead to the development of anxiety and increase the risk of diazepam use and dependence.¹¹⁰

* An analysis of the likelihood of heroin use among smokers versus nonsmokers is unavailable due to small sample size.

† μ -opioid receptors.

‡ Met-enkephalin.

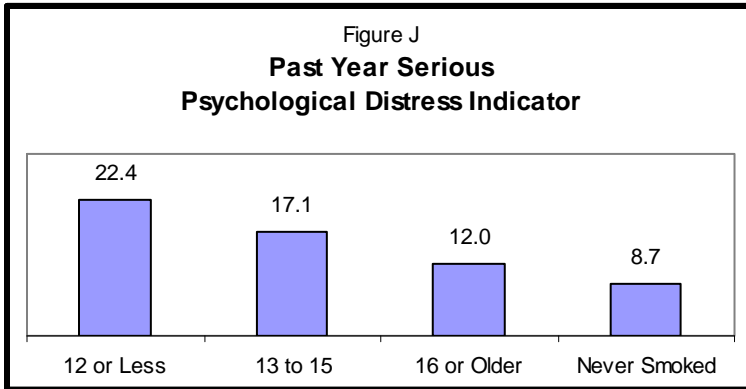
There also is some evidence that nicotine exposure may be linked to Ecstasy use. Ecstasy elicits its pleasurable effects by interacting with the brain systems that use serotonin, a neurotransmitter affected by nicotine exposure.¹¹¹ Research does not yet exist to demonstrate the link between the effects of nicotine exposure on other drugs of abuse.¹¹²

Nicotine and Mental Health Disorders

Smoking rates are substantially higher in people who suffer from a psychiatric disorder as compared with the general population.¹¹³ In some cases, smoking may be a way to self-medicate symptoms of mental illness; exposure to nicotine during adolescence also could elicit specific changes in the brain consistent with increased vulnerability to developing psychiatric disorders later in life. The observed link between smoking and mental illness also may result from common underlying factors.

CASA's analysis of data from the *NSDUH* indicates that those who reported early initiation of smoking were more likely to experience serious psychological distress[§] in the past year. For example, individuals who initiated smoking at age 12 or younger are almost twice as likely to report psychological distress as those who initiated smoking at age 16 or older (22.4 percent vs. 12 percent); early initiators of smoking are more than 2.5 times likelier than individuals who never smoked to report experiencing psychological distress in the past year (22.4 percent vs. 8.7 percent).¹¹⁴ (Figure J)

§ The measure of psychological distress is an index of six variables in the *NSDUH*, for which respondents are asked to think of the one month in the past year when they were the most distressed, anxious or emotionally stressed and to indicate how often during that time they felt nervous, hopeless, restless or fidgety, sad or depressed, that everything was an effort or down on themselves, no good or worthless.



Depression

CASA's analysis of data from the *NSDUH* finds that, among teens ages 12 to 17, twice as many current smokers as nonsmokers had a major depressive episode in the past year (16.8 percent vs. 7.7 percent).¹¹⁵ Likewise, teens who met clinical diagnostic criteria of nicotine dependence in the past 30 days are almost twice as likely as those who are not dependent on nicotine to have had a major depressive episode in the past year (16 percent vs. 8.4 percent).¹¹⁶

Consistent with CASA's analysis, another national longitudinal study found that, compared to nonsmokers or those who started smoking later in life, respondents who began smoking before age 13 had more diagnoses of depressive disorders, were twice as likely to be diagnosed with major depression, had more depressive symptoms and more depressive episodes and were younger at the age of onset of major depressive disorder.¹¹⁷ Another study found that teens who were current smokers and had no symptoms of depression were more than twice as likely to develop depressive symptoms after one year as compared with their nonsmoking counterparts.¹¹⁸ In one study, heavy, long-term smoking among adolescents predicted an increase in depressive symptoms over 18 months, even after controlling for factors associated with youth smoking such as emotional support, substance use by peers and parents and personality factors.¹¹⁹ Among teens with moderate levels of depressive symptoms at baseline, smoking has been linked to a faster rate of intensifying symptoms.¹²⁰

Explaining the link. Animal research provides a possible neurochemical explanation for the finding that tobacco use seems to precede depression in human adolescents. Although the exact mechanism of the relationship is not well understood, the brain chemical serotonin has been implicated in many psychiatric conditions, including depression. Systems of the brain that use serotonin undergo significant developmental changes during adolescence and are uniquely affected by nicotine exposure.¹²¹ Furthermore, the serotonin impairment that is associated with the onset of depressive symptoms in humans* parallels the serotonin impairment observed in adolescent animals' brains following nicotine exposure.¹²² Nicotine exposure in adolescent rats is associated with reduced serotonin in the synapses between neurons in the brain.[†] Lower levels of synaptic serotonin are associated with depressive symptoms.¹²³ When there is a reduction in serotonin emerging from neurons into the synapses, the brain typically increases the number of serotonin receptors to compensate for serotonergic deficits. In people with depression, however, the brain exhibits a *decrease* in these receptors. Animal studies have shown that when adolescent nicotine exposure causes serotonin impairments, a similar pattern of decreasing receptors occurs, suggesting a link between teen tobacco use and risk for depression.¹²⁴

While some evidence points to an increased risk of depression as a result of smoking, the converse relationship also exists.¹²⁵ Some work has identified depressive disorders as risk factors for smoking initiation,[‡] and depression may increase the likelihood of nicotine dependence.¹²⁶ One study of adolescents found that participants with symptoms of depression were more likely to start smoking than their nondepressed counterparts.¹²⁷ Large-scale studies suggest that smoking at a young age is an indicator of a host of social and

* Specifically, the inhibition of 5HT presynaptic activity--i.e., reduced 5HT in the neurons that send chemical messages to other neurons.

† This association is stronger in females than in males.

‡ Alleviation of depressive symptoms may be a motivating factor for cigarette smoking, as nicotine may enhance mood in the short-term.

behavioral problems that contribute to increased risk of depression.¹²⁸

Anxiety Disorders

Anxiety disorders affect almost 20 percent of the population age 18 and older¹²⁹ and smoking is highly prevalent among people with anxiety disorders. Approximately 22 percent of nicotine-dependent smokers suffer from an anxiety disorder compared with approximately 11 percent in the general population.¹³⁰ Smokers with anxiety disorders have more and stronger symptoms of anxiety than nonsmokers with anxiety disorders.¹³¹ Smoking cigarettes at a young age is associated with an increased risk of developing anxiety disorders, including generalized anxiety disorder (GAD),* panic disorder,† phobias‡ and post-traumatic stress disorder (PTSD).§

Generalized Anxiety Disorder (GAD). Research findings among humans have been inconsistent in terms of the direction of the relationship between smoking and GAD. One study found that smoking in adolescence predicts the onset of anxiety disorders; heavy smokers in particular were 5.5 times more likely to develop GAD than smokers who smoked fewer than 20 cigarettes per day.¹³² The relationship between smoking and GAD also may be attributable to factors other than nicotine exposure at an early age. One study found that the greater prevalence of smoking among people with GAD might be due to common genetic vulnerabilities that increase the risk both of tobacco use and GAD.¹³³

* GAD is characterized by chronic anxiety and worrying, often when there is nothing to provoke those emotions.

† Panic disorder is characterized by sudden and recurring episodes of severe fear, and can be accompanied by physical symptoms such as heart palpitations and shortness of breath.

‡ Phobia disorders are characterized by excessive fear of a specific subject or situation that interferes with daily life.

§ PTSD can develop after experiencing a traumatic event such as sexual assault, natural disasters or military combat.

Panic attacks and panic disorder. Up to 40 percent of people with panic disorder smoke cigarettes.¹³⁴ Studies in human adolescents tend to support a temporal progression from early cigarette smoking to panic attacks and panic disorder. One study found that teen daily smokers were significantly more likely than their nonsmoking peers to experience panic attacks or have panic disorder as young adults.¹³⁵ This study further found that panic attacks or panic disorder during adolescence did not increase the risk of smoking initiation, suggesting that the direction of the relationship between smoking and panic is such that early nicotine exposure may increase the risk for panic disorder symptoms later in life.¹³⁶

Another study that followed adolescents through young adulthood found a distinct directional relationship between smoking and panic disorder--a significant increase in the risk for panic attacks or panic disorder by age 21 was shown among participants who were regular smokers as teens.¹³⁷ Other research has shown that adolescents who are heavy smokers are more than 15 times likelier than those who smoke less than a pack of cigarettes per day to develop panic disorder as young adults.¹³⁸

While these findings are consistent with animal studies that suggest the link between smoking and panic disorder may be attributable to neurological changes that follow nicotine exposure, other factors also have been found to contribute to the association. Nicotine causes the release of certain chemicals in the brain** that are associated with increased heart rate and elevated blood pressure, the symptoms of which might be misinterpreted as panic.¹³⁹ Other research suggests that the impaired lung function that results from smoking can trigger panic attacks.¹⁴⁰

A test of animal behavior that measures symptoms of panic disorder†† found that administering nicotine to adult rats in a specific region of the

** Specifically, norepinephrine and epinephrine.

†† The elevated plus maze test measures the time spent in different sections (open arm vs. closed arm) of a maze. It can be used to evaluate panic disorder and specific phobias. More time spent in the open arms of the maze signify less anxiety whereas more time spent in the closed arms of the maze signify more anxiety.

brain* elicited behavior consistent with increased levels of panic.^{† 141} The nature of the link between nicotine and anxiety in adolescent rats, however, appears to be gender specific. In a study in which adolescent rats were subjected to a similar experiment, the results revealed that males demonstrated less anxiety and females demonstrated more anxiety. These findings suggest that females might be more sensitive than males to the increased risk of anxiety that is associated with nicotine exposure.¹⁴²

Phobias. The relationship between early smoking and phobic disorders is less clear than for other psychiatric conditions. One study demonstrated that current smoking among adolescents predicted the onset of agoraphobia;[‡] among former smokers, the risk of developing agoraphobia declined in accordance with time since smoking cessation.¹⁴³ Another study estimated that adolescents who smoked 20 or more cigarettes per day faced a nearly seven-fold increase in the risk of developing agoraphobia as young adults compared to adolescents who smoked fewer cigarettes.^{144, 145} Another study found that when nicotine was administered to specific brain regions,[§] test rats actually exhibited decreases in symptoms of phobias.¹⁴⁶

Post-Traumatic Stress Disorder (PTSD). Of the estimated 70 percent of individuals who will experience a traumatic event at least once in their lifetime, 10 percent will develop PTSD; 60 percent of these individuals smoke cigarettes.¹⁴⁷ The link between smoking and PTSD is strong among adolescents; a study of trauma-exposed adolescent girls revealed that 86 percent of those with PTSD smoked cigarettes, as compared with 31 percent of girls without PTSD.¹⁴⁸ While the relationship between tobacco use and PTSD is complex, some research indicates that nicotine exposure prior to a traumatic event may increase the risk of developing PTSD. Animal studies have shown,

for example, that nicotine exposure in adult rodents causes various changes in the brain that permanently alter their response to stressful environments.¹⁴⁹ A study of twins showed that male adult smokers exposed to trauma were twice as likely to develop PTSD as nonsmokers exposed to trauma; while this was partially attributable to genetics, other factors--particularly changes in the brain that result from nicotine exposure--also contributed to the observed relationship between tobacco use and PTSD.¹⁵⁰

Other research suggests that exposure to trauma during adolescence may increase the risk of smoking; one study found that experiencing a physical assault or witnessing violence doubled the risk of smoking.¹⁵¹ Higher rates of tobacco use among individuals suffering from PTSD also might reflect attempts to self-medicate PTSD symptoms.¹⁵²

Implications for Policy and Practice

Cigarette smoking is the number one preventable cause of death in the United States. Tobacco kills more people in the U.S. each year than alcohol, cocaine, crack, heroin, AIDS, suicide, automobile accidents and fires *combined*.¹⁵³ The physical consequences of cigarette smoking--such as cancers, cardiovascular illnesses, respiratory diseases and reproductive problems¹⁵⁴--have been well known for years.

Teen smokers are at risk for a whole host of physical problems during adolescence. Compared with nonsmokers, teens who smoke are less physically fit, and have retarded lung growth and diminished lung function. Young smokers frequently report such symptoms as wheezing, shortness of breath, coughing and an increase in phlegm production. In general, teen smokers have a greater susceptibility to respiratory diseases than nonsmokers. And because they tend to be less physically fit, teen smokers suffer in terms of physical performance and endurance.¹⁵⁵

* The lateral septum.

† Decreased time spent in the open arms of the maze.

‡ Fear of experiencing a difficult situation from which one cannot escape. This phobia may lead the sufferer to avoid spaces or situations associated with anxiety and, in severe cases, to be confined to his or her home.

§ The dorsal hippocampus and lateral septum.

The latest research discussed in this White Paper adds to the long-established consequences of tobacco use, and puts to rest any question about the profound harm associated with early exposure to nicotine. The powerful connection between early initiation of smoking and heightened risk for alcohol and illicit drug use and abuse and certain mental disorders, as well as the substantial social and economic burden associated with each of these conditions, highlights the tremendous public health problem of youth tobacco use and the urgent need to prevent and reduce it.¹⁵⁶ The public health case is clear. It is now time to act.

Because tobacco products constitute substances hazardous for purposes of human consumption, CASA recommends strong public action to help reduce the enormous risks of youth smoking. Medical and other scientific evidence now justifies the following recommendations:

- Sharply restrict all tobacco advertising, marketing and promotion of tobacco products.
- Give the U.S. Food and Drug Administration comprehensive authority to regulate tobacco products.
- Continue and expand strong, evidence-based counter-advertising efforts.
- Step up federal and state funding of comprehensive, evidence-based smoking prevention and cessation programs.
- Mandate evidence-based tobacco cessation in substance abuse treatment and mental health care settings.
- Increase enforcement of laws restricting the sale of tobacco products to minors, including routine retailer compliance checks and harsher penalties for violators.
- Enact strong indoor and outdoor clean air laws to limit children's exposure to environmental tobacco smoke.
- Alert parents, healthcare professionals, teachers and others responsible for young people to prevent youth smoking; intervene to

stop it; and understand that youth tobacco use may signal mental illness and alcohol and other drug use that require intervention and possibly treatment.

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