



Nicotine: How Does it Affect Health?

Background

Of the more than 7000 chemicals in tobacco smoke, nicotine is one of the most widely assessed. Nicotine has been identified as the primary substance in tobacco that causes addiction and, as such, the main substance driving use of tobacco products.¹ For many years, most of the harm associated with tobacco has been attributed to other substances in tobacco, and particularly tobacco smoke, such as nitrosamines and polycyclic aromatic hydrocarbons (PAHs). Nevertheless, recent research suggests that there are significant and substantial health effects associated directly with nicotine. The rise of commercial products that deliver nicotine without tobacco smoke make it important to assess the potential risks of nicotine in both traditional and alternative tobacco products.

Key Finding: Recent research suggests that there are significant and substantial health effects associated directly with nicotine.

The investigation of the health effects of nicotine in humans is challenging, and much of the evidence of harms at this point comes from animal studies. A major review by the Surgeon General of the United States in 2014 summarized the literature on the health effects of nicotine on both humans and laboratory animals.² A more recent report from the US Surgeon General on electronic cigarettes updates the research on the health effects of nicotine in youth.³ In this update, we build on these previous reports by reviewing data on the potential health risks associated with nicotine specifically. Most health effects of nicotine are seen at or below typical doses of nicotine for cigarette smokers or nicotine e-cigarette vapers.²

Nicotine is Addictive

Nicotine is the major component in tobacco products that is responsible for addiction.^{4,5,6,7,8} The risk for nicotine addiction depends on the dose of nicotine delivered and how quickly and by what route it is delivered. The potential for addiction increases with the dose delivery rate, the rate of absorption, and the concentration of nicotine attained.^{9,10,11} The pharmacologic reasons for nicotine use include perceived mood enhancement and relief of withdrawal symptoms.¹² Because many nicotine products are designed to maximize its addictive potential, nicotine is also intimately tied to the non-nicotine health effects resulting from the use of conventional and alternative nicotine products.

Nicotine is a Poison

Nicotine in large doses can be toxic because it affects the functioning of the parasympathetic autonomic nervous system.¹ Smaller doses may cause nausea, vomiting, diarrhea, increased salivation, increased respiratory secretions, and abnormally low heart rate.² Larger doses that may cause seizures and death and fatal poisoning have been regularly reported in the literature, primarily associated with its use as a pesticide. A fatal dose of 50-60 mg for an adult is commonly cited in the literature, but a more accurate fatal dose may be at least 500 mg;¹³ however, 6mg of nicotine could be fatal for a child.¹⁴

Nicotine May Contribute to Cancer Risks

The Surgeon General of the United States concluded in 2014 “There is insufficient data to conclude that nicotine causes or contributes to cancer in humans, but there is evidence showing possible oral, esophageal, or pancreatic cancer risks.” Animal and clinical studies suggest that nicotine might play a role in the spread of cancer, as it appears to act as a tumor promoter increasing the rate of metastases.¹⁵ Nicotine could also reduce survival because it stimulates cell motility and migration and loss of adhesion, thereby changing a well-differentiated epithelial cell to a highly invasive carcinoma. It can also promote the development of new blood vessels.² At this point, there is insufficient evidence to suggest that nicotine directly causes cancer.^{2,16,17,18,19,20} In human studies, the use of smokeless tobacco is associated with increased risk of some cancers; however, risks vary by type of smokeless product, suggesting that tobacco specific carcinogens may be even more important contributors to cancer than nicotine.²¹ Follow-up analysis of the Lung Health Study found no excess cancer risk among long-term nicotine replacement users.²²

Nicotine May Contribute to Cardiovascular Disease

Nicotine has been implicated in the onset of heart attacks and in causing the formation of arterial plaque.² Nicotine has well known effects on the sympathetic nervous system as it increases heart rate and myocardial contractility, increases coronary vascular resistance, and reduces insulin sensitivity.² In addition, a number of other potential mechanisms for the role of nicotine on cardiovascular disease exist that suggest that nicotine may also affect formation of arterial plaque.^{23,24} However, there are still gaps in our understanding of the specific impacts and cardiovascular risks of nicotine use.

Nicotine Affects Immune Function

Nicotine can suppress immune system functioning and interfere with immunological diseases.² There is good evidence that nicotine affects cellular immunity, either directly by interacting with nicotinic cholinergic receptors or indirectly via its effects on the nervous system.²⁵ Furthermore, nicotine suppresses the production of antibodies and immune system cells (B and T) in the blood.²⁶ It is still unclear whether this contributes to the overall adverse effects of cigarette smoke on immunity.

Nicotine Causes Fetal Damage

Nicotine causes or is suspected to cause a wide variety of health effects on pregnancy outcome and on the fetus, including fetal growth restrictions, preterm delivery, stillbirth, perinatal mortality, orofacial clefts, clubfoot, cryptorchidism, gastroschisis, some types of congenital heart defects and sudden infant death syndrome.² These experimental studies have been conducted *in vitro* primarily using nicotine alone, as well as some *in vivo* studies of cigarette smoking by pregnant women compared to women using smokeless tobacco.^{27,28} Smoking during pregnancy is also strongly associated with impaired lung development in infants, and evidence suggests that nicotine plays a direct role here.^{2,29,30} Nicotine exposure is also associated with a reduction in fertility in offspring³¹ and with obesity and Type 2 diabetes among offspring.^{32,33}

Nicotine Affects the Developing Adolescent Brain

There is now considerable evidence from both animal and human studies that nicotine negatively affects both adolescent and prenatal brain development.^{2,34} Animal studies and functional magnetic imaging studies have shown nicotine exposure during adolescence appears to cause long term structural and functional changes in the brain.³⁵ Major changes in brain development occur in childhood and particularly in adolescence up to about age 25, the critical years for the onset of nicotine use. Human adolescents appear to be particularly vulnerable to drug-seeking behaviour, attention deficits and mood disorders,³ and nicotine can promote these behaviours and conditions. Rodent models suggest that nicotine exposure affects reward learning, which can enhance the effects of other drugs of abuse.

Nicotine is Associated with Mental Illness

The Surgeon General suggests that there is no established role for nicotine in any treatment of mental illness.² Moreover, there are indications that nicotine may play a role in the onset or worsening of mental illness. One meta-analysis found that prior smoking was associated with

the onset of depression.³⁶ There are further indications that smoking is associated with increases in rates of suicide.³⁷ There is also increasing evidence of cognitive deficits from smoking among those with serious mental illness.³⁸

Among nicotine-addicted smokers, abstinence from smoking is associated with reductions in negative affect. Further, one meta-analysis of studies of adults found that depression and mood improved consistently after quitting smoking.³⁹

The US Surgeon General³ concluded that nicotine exposure during adolescence probably contributes to mental health disorders. Adolescents with mental health disorders are more likely to start smoking and to develop long-term dependence on nicotine.

Discussion and Conclusions

The overall health impact of nicotine cannot be assessed separately from the environmental context in which it is used. Nicotine products are available commercially, are marketed with varying levels of regulation, and are subject to age restrictions that can be difficult to enforce. Use and exposure to nicotine are influenced by social norms, by restrictions on where nicotine products can be used, and by the types of products and method of use. Social cues for use can increase consumption and lead to relapse after cessation.

To assess the public health effects of nicotine, it is important to go beyond effects on individuals and look at the net effect on populations. The tobacco industry has long claimed that they are in the nicotine business, not the cigarette business. Thus, a full discussion of the health impact of nicotine needs to involve the potential for deregulation and promotion of nicotine products believed to be less harmful as well as other factors that could lead to increased use and potential normalization of both new and existing products.

The evidence to date suggests that nicotine is not harmless and that apart from its role in addicting tobacco users, nicotine is responsible for a range of negative health effects. New research should include examining substances that may be added and formed or changed by heating in alternative nicotine products. These include flavourings and other chemicals that make nicotine more appealing or better-absorbed and other drugs, such as marijuana, which is frequently mixed with nicotine or tobacco. This research will be complex and difficult but will lead to a better understanding of the impact of nicotine on humans from the prenatal period to old age.

Authors: Roberta Ferrence, Michael Chaiton, Robert Schwartz

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