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Public Health

The Direct Effects of Nicotine Use on Human Health

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Abstract

Tobacco is one of the leading preventable causes of death in the United States. The role of some of the specific components of tobacco and tobacco pyrolysis in causing human disease has been well described. However, the health risks attributable to *nicotine alone* have not been fully determined, especially for long-term use. Nicotine is a potent chemical that has

powerful effects on the human body, especially when administered rapidly or at high doses. Although many of these effects are deleterious, others may be beneficial. In certain special populations, such as the developing fetus, or persons with significant cardiovascular disease, nicotine has greater adverse effects. Because of the recent emphasis on using nicotine to treat tobacco dependence, as well as the interest in using nicotine as a possible agent for reducing overall tobacco use, clarifying the effects of long-term nicotine use on human health is important.

Introduction

Tobacco use has been linked to a variety of human illnesses^{1,2} ranging from cancer and cardiovascular disease to premature birth and peptic ulcer disease. The specific contributions of the components of tobacco to morbidity and mortality are debated, but the products of combustion, particularly the polynuclear aromatic hydrocarbons and carbon monoxide, are

thought to play major roles³. Through its addictive properties, nicotine is a significant cause of continuing tobacco use.^{4,5,6} However, the direct, human health effects of nicotine use alone have not been well delineated. Although its pharmacologic and addictive properties have been well described, less has been written on the direct human health effects of nicotine.

Recently, "safer" ways to deliver nicotine to smokers have been discussed. For example, some researchers have suggested that smokeless tobacco could be a safer alternative for persons who will not or cannot stop using tobacco, because the users of smokeless tobacco -- and those around them -- would not be exposed to the products of tobacco combustion.⁷ Although smokeless tobacco products do achieve the goal of delivering -- without combustion -- nicotine to the brain, these agents have also been associated with a number of tobacco-induced

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systemic and local adverse health outcomes,⁸ arguing against their use as substitutes for cigarettes.

A second, "safer" form of nicotine recently proposed is the smokeless cigarette.⁹ This nicotine-delivery device was briefly test-marketed in the mid-1980s. The tobacco industry is currently considering a second-generation smokeless cigarette product for test-marketing. The US Food and Drug Administration (FDA) has raised appropriate concerns about the need to regulate such smokeless cigarette products as drug delivery systems.

Two other forms of nicotine-replacement therapy (nicotine gum and the nicotine patch) have been approved by the FDA as a prescription aid for smoking cessation. Recent meta-analyses^{10,11} have deemed these products both safe and effective in the treatment of tobacco addiction. Finally, nicotine delivery systems such as nicotine nasal spray, vapor inhaler, and lozenges are currently under study.¹²

In light of the recent interest in nicotine among health-care providers, regulatory agencies, and the general public, both as a therapeutic aid for assisting smoking cessation and as an addictive drug, a review of what is known about the direct human health effects of long-term nicotine use is important to offer guidance to physicians, policy makers, and consumers.

The addictive properties of nicotine, although an important cause of tobacco addiction and subsequent health problems, will not be discussed in this report. Similarly, the acute effects of nicotine (e.g., nicotine poisoning⁴ and "green-tobacco syndrome"¹³) will not be discussed further.

We will first describe nicotine's structure and metabolic and physiologic effects, then review facts relating to the role of nicotine

in human disease. Finally, we will report nicotine's effects in special populations.

NICOTINE: STRUCTURE AND METABOLISM

The structure and function of nicotine have been extensively described in the literature.¹⁴ In brief, nicotine in tobacco exists mainly as a water- and lipid-soluble alkaloid, a tertiary amine composed of a pyridine and a pyrrolidine ring (figure 1). Its uptake via inhalation (e.g., cigarette smoking) or across mucous membranes (e.g., smokeless tobacco) is rapid; absorption is pH dependent.¹⁵ Once absorbed, it is distributed extensively throughout the body. It freely crosses the placenta. Nicotine readily crosses the blood-brain barrier and is distributed throughout the brain.¹⁴

Nicotine is metabolized in the liver and lung, although some is excreted unchanged in the urine. The primary metabolites are cotinine and nicotine-*N*-oxide, both pharmacologically inactive.¹⁵

NICOTINE: PHYSIOLOGIC EFFECTS

The physiologic effects of nicotine have been well studied, both in the laboratory and in controlled clinical settings. An overview of these effects is helpful for understanding the health effects of nicotine use. Table 1 summarizes nicotine's

physiological effects and potential risks and benefits by organ system.

Central nervous system

Nicotine acts on binding sites or receptors throughout the nervous system, interacting with specific receptors. Nicotine appears to have a stimulant effect on the central nervous system, as shown in a variety of animal and human studies.⁴ It appears to be capable of stimulating the release of several pituitary and hypothalamic hormones. In addition, nicotine might alter brain energy metabolism and electrophysiology.⁴

Cardiovascular system

Nicotine stimulates autonomic ganglia and skeletal neuromuscular junctions throughout the body by binding to acetylcholine receptors. It also appears to stimulate the sympathetic nervous system via the adrenal medulla.¹⁵ This stimulation can lead to increased heart rate, myocardial contractility, and vascular tone, as well as greater platelet aggregation and altered lipid and fatty acid metabolism.¹⁶

Pulmonary system

Nicotine has significant effects on the bronchial epithelium, increasing vascular and cellular permeability, inducing an inflammatory response, and affecting repair mechanisms.⁴

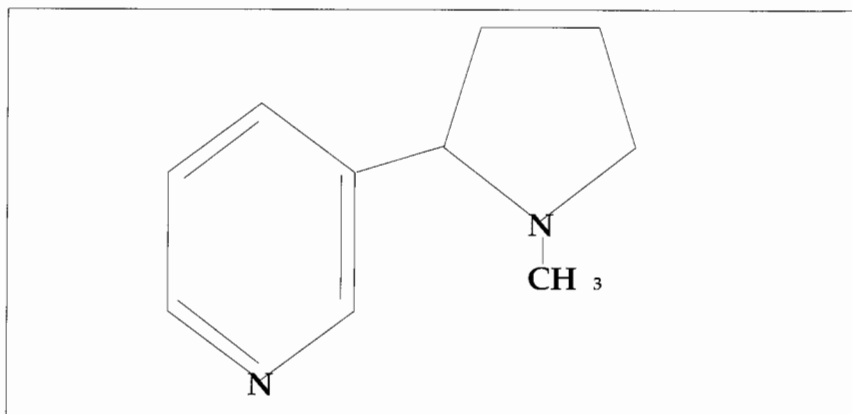


Fig 1. Structure of nicotine

Table 1: Human Health Effects of Long-Term Nicotine Administration

Organ System	Physiologic Effects	Potential Risks and Benefits
Central Nervous System	<p>Binds to a variety of receptors Overall stimulant effect</p> <p>Stimulates release of several hypothalamic and pituitary hormones Alters electrophysiology and psychophysiology reactivity</p>	<p>Might cause sleep disturbance Might cause sleep apnea --might be protective</p> <p>Associated with Alzheimer's disease and tardive dyskinesia Might be protective for Parkinson's disease</p>
Cardiovascular System	<p>Increases heart rate, contractility, vascular tone</p>	<p>Might worsen pre-existing coronary artery disease Might exacerbate arrhythmias Might worsen peripheral vascular disease</p>
Pulmonary System	<p>Increases vascular and cellular permeability Induces inflammatory response Affects repair mechanisms</p>	<p>Might play a role in airways disease</p>
Gastrointestinal System	<p>Increases basal acid secretion Decreases mucosal blood flow Inhibits mucosal prostaglandin synthesis Reduces pancreatic bicarbonate secretion</p> <p>Reduces lower esophageal and pyloric sphincter pressures Lowers motility</p>	<p>Might be a factor in peptic ulcer disease Might cause delayed ulcer healing Might cause esophagitis Might be protective or a therapeutic aid for ulcerative colitis</p>
Endocrine and Reproductive Systems	<p>Alters hormone production Affects placental blood flow</p>	<p>Might reduce birth weight Might affect developing nervous system</p>
Other	<p>Increases platelet aggregation Alters lipid and fatty acid metabolism</p> <p>Stimulates adrenal cortex and medulla Increases catecholamine release</p>	<p>Might delay skin wound healing Might exacerbate hyperthyroidism or insulin-dependent diabetes mellitus</p>

Gastrointestinal system

Data from several animal studies have indicated mechanisms by which nicotine affects the gastrointestinal system. These mechanisms include increasing basal acid secretion, reducing pancreatic bi-

carbonate secretion, inhibiting mucosal prostaglandin synthesis and decreasing mucosal blood flow, and lowering esophageal and pyloric sphincter pressures. Further, nicotine might reduce gastrointestinal motility.⁴

Endocrine system

Nicotine exerts effects on nearly all components of the endocrine and neuroendocrine systems, including catecholamines, corticosteroids, serotonin, and several pituitary

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hormones. Some of these effects are mediated through the hypothalamic-pituitary axis; some are produced by direct effects on the adrenal cortex and medulla.⁴

Other physiologic effects

Nicotine can produce skeletal muscle relaxation, or it can enhance tension. It can also alter psychophysiologic reactivity.⁴

NICOTINE:

HUMAN HEALTH EFFECTS

The *in vivo* actions of nicotine are complex and depend on dose, method and rapidity of administration, target organ, prevalent autonomic tone, and prior exposure history. Thus, the actual human health effects and diseases resulting from nicotine use are not straightforward. These health effects are summarized in table 1.

Central nervous system

The consequences of long-term, nicotine-induced central nervous system stimulation are unclear. Sleep disturbances and sleep-disordered breathing, both observed in smokers, may be due in part to the stimulant effects of nicotine¹⁷ or to nicotine withdrawal. Others have suggested that nicotine might protect against sleep apnea.¹⁸

Nicotine has been both positively and negatively associated with psychological disorders, including schizophrenia and Tourette's syndrome. Nicotine might increase the risk of Alzheimer's disease and tardive dyskinesia, but appears to reduce the risk of Parkinson's disease.¹⁹

Cardiovascular system

The action of nicotine on the heart and blood vessels has been studied extensively. Through its effects on heart rate and myocardial contractility, vascular tone, catecholamines, coagulation and platelet ag-

gregation, as well as lipid and fatty acid metabolism, nicotine may contribute to the coronary heart disease caused by cigarette smoking, and may play a role in acute coronary events.¹⁶ However, the long-term cardiovascular health effects of long-term nicotine use are not well understood.

A study of Swedish construction workers indicated that smokeless tobacco users had a higher risk of death from cardiovascular disease, though lower than the risk for smokers.²⁰ However, another study from Sweden did not indicate an increased risk of death from myocardial infarction among persons who used smokeless tobacco compared with non-smokers.²¹ Further, animal models have not consistently demonstrated nicotine's adverse cardiac effects.

Some authors^{16,22} have postulated that the effects of nicotine on the cardiovascular system might be a function of the dosing modality, the rapidity with which peak blood levels of the drug are achieved, or tolerance. For example, smoking cigarettes results in a more rapid increase in and higher absolute levels of plasma nicotine than that achieved by chewing nicotine gum²³ or applying the nicotine patch.²⁴ Rapidly increasing blood levels of nicotine achieved by smoking cigarettes exacerbate the acceleration of heart rate and increase in blood pressure produced by nicotine.²² These findings might explain the differences that exist between short-term animal and human studies and long-term human health effects.

The role of nicotine in hypertension is similarly supported by the known pharmacological actions of nicotine, but not well documented in animal or human studies.²⁵

Theoretically, nicotine's potentially hypertensive actions and vascular effects could increase the risk of stroke.¹⁶ However, this theory has not been studied adequately.

Pulmonary system

Nicotine's effects on bronchial epithelium suggest that nicotine can play a role in the development of chronic lung disease, although this claim remains unclear. Studies have suggested that nicotine alone can increase airway resistance, which worsens pulmonary function in persons with existing lung disease.⁴

Gastrointestinal system

Cigarette smoking is a risk factor for peptic ulcer disease, as well as for delayed healing, therapeutic failures, and relapse of ulcers. Nicotine's effects on the gastrointestinal system, including increasing acid secretion while decreasing bicarbonate secretion, prostaglandin synthesis, and mucosal blood flow, might account for these findings. Further, nicotine's ability to reduce lower esophageal and pyloric sphincter pressures might lead to reflux esophagitis.⁴

The route by which nicotine is administered could affect ulcer formation. Local effects of nicotine might be a factor, since orally ingested nicotine, particularly via nicotine gum, can lead to higher gastric levels than inhaled or transdermally absorbed nicotine.⁴

Nicotine possibly protects smokers against the development of ulcerative colitis; some studies indicate that smokers have a lower incidence of this disease^{18,26}.

Other health effects

Nicotine's role as a carcinogen or co-carcinogen is controversial. Although some studies have suggested that nicotine and its primary metabolites might possess weak tumorigenic activity, others have failed to demonstrate carcinogenic properties. Data from a study of Swedish construction workers indicate no increase in cancer mortality among smokeless tobacco users.²⁰

Nicotine might act as a co-carcinogen, but this has not been con-

sistently demonstrated in laboratory experiments. During processing and pyrolysis of tobacco, nicotine can be converted to N-nitrosamines, which are known carcinogens. Whether nicotine-derived nitrosamines contribute significantly to the cancer risks of tobacco smoking is unclear.⁴

The relationship between smoking and delayed wound healing is well recognized.²⁷ Nicotine, as a vasoconstrictor, can impair skin blood flow, which adversely affects wound healing. Further, nicotine-induced platelet aggregation might cause microvascular occlusions and ischemia in compromised tissues.

Recent reports have suggested that nicotine patches and nasal spray can produce local irritation, although the contribution of nicotine itself to these effects has not been determined.^{28,29}

NICOTINE: EFFECTS IN SPECIAL POPULATIONS

Nicotine has different physiologic and health effects in certain individuals. Some persons are at higher risk for adverse health effects than others. These high-risk populations or conditions include developing fetuses, persons with a history of unstable coronary artery disease, and persons with other pre-existing diseases (table 2).

The developing fetus

The relationship between smoking and low birth weight, prematurity, and miscarriage has been well established³⁰, although nicotine's role in these conditions is unclear. Nicotine might be a factor in low birth weight—the level of maternal serum cotinine correlated with reduced birth weight in one study.³¹ Nicotine's effects on the vascular system, which might affect placental development and sufficiency, could be an explanation for some of the reproductive problems caused by cigarette smoking.

Although nicotine adversely af-

Table 2: Potential High-Risk Conditions for Adverse Effects from Nicotine Use

Recent, significant cardiovascular disease
 Significant cardiac arrhythmias
 Accelerated hypertension
 Peripheral vascular disease
 Vasospastic disease
 Active peptic ulcer disease
 Hyperthyroidism
 Insulin-dependent diabetes mellitus
 Pheochromocytoma
 Pregnancy and developing fetuses

See references 16,28.

fects fetal development in some animal models, its association -- and that of cigarette smoking -- with human congenital malformations is unclear. Still, the FDA has classified the nicotine patch as a Category D (positive evidence of human fetal risk) substance.²⁸

Nicotine might have an adverse effect on the developing brain and nervous system *in utero*^{32,33}, leading to behavioral or electrophysiologic alterations .⁴

Persons with pre-existing cardiovascular disease

Studies have reported that patients with stable coronary artery disease can safely use the nicotine patch.^{28,34} However, isolated cases of acute myocardial infarction among persons with coronary artery disease who smoked while using the nicotine patch have been reported.^{28,35} Other researchers have reported that nicotine affects the cardiovascular system of persons with coronary artery disease differently than that of healthy persons.¹⁵ Cases of cardiac arrhythmias, particularly atrial arrhythmias, have been reported in persons who use nicotine gum.⁴

Although smoking does not appear to be a risk factor for the development of chronic hypertension, progression of chronic hyper-

tension to accelerated hypertension or the exacerbation of hypertension caused by pheochromocytoma has been documented in the setting of tobacco use. This has been postulated to occur through nicotine's effects on vascular tone, renal blood flow, or sympathetic nervous system activity.⁴

Researchers believe that nicotine exacerbates Buerger's disease (thromboangiitis obliterans), a vasospastic disorder primarily affecting the extremities.³⁶

Persons with other pre-existing diseases

Nicotine appears to have effects on the endocrine system which may have implications for persons with certain diseases. For example, by stimulating catecholamine release from the adrenal medulla, nicotine may adversely affect persons with hyperthyroidism or insulin-dependent diabetes mellitus.^{4,37}

Conclusion

Nicotine is under intense scrutiny, both because it is the addictive substance in cigarettes and because of its role as a therapeutic agent to aid tobacco dependence. The distinction between tobacco use and nicotine use deserves emphasis

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particularly since some authors have advocated smokeless tobacco as a "safer" form of nicotine, a position not supported by data.

Nicotine is a potent chemical that has powerful effects on the human body, especially when administered rapidly or at high doses. Although many of these effects are deleterious, others may be beneficial. In aggregate, the health effects of long-term administration of nicotine alone are less harmful than the effects of long-term tobacco use. Many of the diseases linked to long-term nicotine use in humans are not life-threatening and are curable or at least treatable. Because of the uncertainty about long-term nicotine exposure, however, future research and review by the U.S. Food and Drug Administration is appropriate. This research is of current importance because nicotine-replacement therapy is now an over-the-counter product.

In certain populations (e.g., pregnant women and persons with unstable coronary artery disease) nicotine should be used only after careful consideration. However, as Benowitz and Hughes have suggested, and from a "harm reduction" perspective, the unequivocal risks of smoking must be weighed against the potential risks of using nicotine alone.^{37,38,39}

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