

CARDIOVASCULAR, CARCINOGENIC AND REPRODUCTIVE EFFECTS OF NICOTINE EXPOSURE

A narrative review of the scientific literature

Javier Martinez and Leonie Price

PubMed reference:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7308884/>

Leonie.Price@jti.com



Agenda

1. Introduction
2. Acute effects of nicotine exposure
3. Cardiovascular (CV) effects of nicotine exposure
4. Carcinogenic effects of nicotine exposure
5. Reproductive effects of nicotine exposure
6. More recent key papers
7. Wrap up

Introduction

Aim of the research

- Investigate potentially pathogenic roles of nicotine exposure
- Provide an overview of the research up to February 2019 across four physiological systems: Acute toxicity, CV risk, Carcinogenesis, Reproduction
 - These areas are known to be particularly vulnerable to the effects of cigarette smoke
 - Nicotine has been hypothesized to play a role in disease pathogenesis

Difficulties in analyzing the research

- Human research into the effects of nicotine is often based on cigarette smokers
- The mode of nicotine delivery leads to different physiological responses
- Blood nicotine concentration is often not measured
- Studies on e-cigarettes are affected by device generation

Acute effects of nicotine exposure

- **Symptoms of acute nicotine toxicity include:**
 - nausea, vomiting, headache, abdominal cramps, breathing difficulty, abnormal body temperature, pallor, diarrhea, chills, fluctuations in blood pressure and heart rate, sweats and increased salivation
- **Current estimation of the lethal dose of ingested nicotine is not based on reliable research**
 - 60 mg of ingested nicotine is widely accepted as the lethal dose for an adult human
 - 60 mg is the level of nicotine found in about 6 cigarettes
- **New products, such as e-cigarettes (ENDS), pose a challenge for preventing nicotine poisoning**
 - Children are at the most risk of accidental ingestion
 - Overall, reported poisoning cases are far lower than the prevalence of e-cigarette use would suggest likely

CV effects of nicotine exposure

- **Nicotine acts on the CV system primarily through stimulation of the sympathetic nervous system via nicotinic acetylcholine receptor (nAChR)**
- **Nicotine exposure leads to short-term, transient increases in blood pressure and heart rate**
- **CV effects of long term nicotine exposure are less clear**
- **Current studies indicate that the nicotine delivered by e-cigarettes does not increase the risk of CV events in individuals who do not have any underlying CV disease**

Cardiovascular effects of nicotine exposure

Key paper:

Polosa R, Cibella F, Caponnetto P, *et al.*: **Health impact of E-cigarettes: a prospective 3.5-year study of regular daily users who have never smoked.** *Sci Rep.* 2017; 7(1): 13825.

- Polosa *et al.* followed a small group (n = 9) of e-cigarette users who had never smoked over a period of 3.5 years
- After 3.5 years, there were no changes to any of the CV parameters measured (heart rate, systolic or diastolic blood pressure) in any of the participants, including those who used the nicotine-containing e-liquid (n = 6)
- The participants were all young and healthy and therefore were not at high risk of CV outcomes
- Suggests that the long-term CV risks in healthy users are limited

Carcinogenic effects of nicotine exposure

- **Nicotine is not a direct or complete carcinogen**
 - There is no evidence to suggest that nicotine is a complete carcinogen (i.e., causes tumor initiation, promotion and progression)
- **Several documents issued by authoritative bodies also state that nicotine is not considered a carcinogen.**
 - E.g., Surgeon General, FDA, Royal College of Physicians
- **It is not clear whether nicotine has a role in cancer propagation and metastasis**
 - Pathways have been proposed using molecular techniques
 - No studies have demonstrated the mechanisms *in vivo*

Carcinogenic effects of nicotine exposure

Key paper:

Araghi M, Rosaria Galanti M, Lundberg M, *et al.*: **Use of moist oral snuff (snus) and pancreatic cancer: Pooled analysis of nine prospective observational studies.** *Int J Cancer.* 2017; 141(4): 687–693.

- Analysis of nine cohorts of men across Sweden, totaling 418,448 participants from 1978 to 2013
- No increase in the incidence of pancreatic cancer found in snus users
- “Our findings, from the largest sample to date, do not support a role of snus use in the development of pancreatic cancer in men”

Reproductive effects of nicotine exposure

- **Research about the effect of nicotine on fertility in humans is lacking**
 - Nicotine is found in the seminal fluids of male daily smokers
 - Cotinine can be detected in the follicular fluid of women exposed to cigarette smoke
- ***In utero* nicotine exposure could be important for fetal development**
 - Evidence provided by animal studies suggests that nicotine itself is likely to be detrimental to fetal lung and brain development
 - Nicotine exposure during development may lead to long-term changes to nicotinic receptor distribution in the offspring, and downstream neurological alterations
 - The FDA deem nicotine as a category D drug:

“For pregnancy category D, if there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks”

Reproductive effects of nicotine exposure

Key paper:

Sekhon HS, Jia Y, Raab R, *et al.*: **Prenatal nicotine increases pulmonary alpha7 nicotinic receptor expression and alters fetal lung development in monkeys.** *J Clin Invest.* 1999; 103(5): 637–647.

- Rhesus monkeys were dosed with nicotine at 1.0 mg/kg/day, using an osmotic pump, from day 26 of gestation until birth
- Alveolar airspace was significantly increased, and corresponding surface area was decreased in nicotine-exposed offspring compared to controls
- The number of nicotinic receptors was significantly increased in cells lining the airway walls of nicotine-exposed offspring, suggesting that nicotine induced the upregulation of its receptor in the lung tissue
- The authors hypothesized that the increase in nicotinic receptors they observed in fibroblasts could lead to an increase in collagen deposition within the lung

More recent papers

Acute Toxicity:

Alkam, T. and Nabeshima, T. (2019). *Neurochem Int*, 125:117–126

- Japanese researchers published a review analyzing the molecular mechanisms behind acute nicotine toxicity. The authors explored how nicotine toxicity arises through the stimulation of various nicotine receptor (nAChR) subunits but realised that there are still many areas requiring further investigation. They suggest that "...[F]uture studies should answer questions such as synaptic nicotine degradation and specific subunits of nAChRs that involved in the various toxicity of nicotine".

Carcinogenesis:

Wang, M. *et al.* (2019). *Onco Targets Ther*, 12: 3327-3338

- This mouse study investigated whether nicotine could affect how cancer spreads from one organ or tissue to another. They found that mice had a higher rate of cancer-spread when they were treated with nicotine compared to mice that were not treated. They also found that a specific gene (*Prx1*) may be involved in the process. This study might not be relevant to human cancer as diseases behave differently in humans and mice; however, it adds new understanding into how cancer spreads.

CV effects:

Jensen, K.P. *et al.* (2020). *Phycopharmacology*

- Scientists from America investigated whether the speed of nicotine delivery influenced heart-rate, blood pressure and perceived nicotine effects in smokers. They found that the speed of nicotine delivery, not just the amount has an effect on how nicotine reduces withdrawal symptoms. Heart rate and blood pressure were also affected differently by the speed of nicotine delivery.

Reproductive effects:

Mimose-Sato, Y. and Sato, K. (2020). *IBRO Reports* 9:14–23

- Scientists exposed chicken embryos to nicotine whilst developing in the egg, and observed their neurological development. It is important that this study should not be used to speculate on human developmental effects as the species differences are too great and the exposure method is artificial; however, the authors found that the nicotine-exposed chicks showed different movement patterns as they grew. The authors suggest that this effect is exerted through nicotine interacting with nAChRs in the developing neurological tissue.

Wrap-up

Acute effects

Acute toxicity from nicotine is highly unlikely to occur when ENDS are used as intended by adults

CV effects

The long-term CV consequences of nicotine exposure are not known

Currently, the literature suggests that in consumers with no underlying cardiovascular pathology, there is no increased CV risk due to nicotine exposure

Carcinogenic effects

Nicotine is not a direct or complete carcinogen

It is not yet clear whether it has a role in cancer propagation and metastasis

Reproductive effects

Further studies are needed to determine whether nicotine is detrimental to fertility in humans

Animal studies indicate that nicotine has many and wide-ranging effects on fetal development