CLINICAL REVIEW

Nicotine: A Cause for Concern?

Garrett Harada, B.A., and Holly R. Middlekauff, M.D.

Introduction

Nicotine is one of the most widely consumed psychoactive compounds today. However, little is known about the health effects of nicotine alone, since most research to date has been focused on nicotine in its combusted form, for example, in tobacco cigarettes. With the recent surge in popularity of non-combusted forms of nicotine, such as electronic cigarettes and snus, a Swedish smokeless tobacco, which are purported to be safer than lethal tobacco cigarettes, a review of the health effects of nicotine is timely. For example, snus has been shown to possess a similar nicotine content but significantly lower health risks, compared to tobacco cigarettes.[1,2] In addition, recent studies have also shown that electronic cigarettes likely possess significantly reduced risks as well.[3] Though this suggests that most of the harm may lie in the consumption of combusted or ingested particulates outside of nicotine, the long-term health effects of these alternative nicotine-delivery methods, including nicotine replacement therapies (transdermal or gum) remains unknown. In fact, some studies have actually proposed mechanisms by which exposure to nicotine, the alkaloid found in each of these products, may have negative health consequences.[4] In this paper, we will review what is known about the health effects of nicotine, highlighting potential causes for concern as well as areas worthy of future investigation.

Current State of Nicotine Literature

Studies of nicotine-containing products abound, but many are not focused on the potential harms of nicotine instead focusing on the other compounds in nicotine products, including the particulates in tobacco smoke, or the additives and flavorings in electronic cigarettes. With the observation that "nicotine addicts, but it is the tar that kills," which led to the development of nicotine replacement therapies as an aid to smoking cessation, nicotine has been perpetuated as a relatively harmless character.[5] Nonetheless, it is worth considering the possibility that nicotine, especially aerosolized nicotine, may not be as benign as previously believed.

For instance, many studies show that nicotine may have roles in promoting apoptosis and neoplasia through reactive oxygen species and enhancement of epithelial to mesenchymal transitions respectively.[6,7] In addition, cotinine, the major metabolite of nicotine, which has been believed to be physiologically inert, may have additional metabolic activity. Cotinine may desensitize ganglionic nicotinic receptors, inhibit wound repair, induce cell proliferation through telomerase reactivation, and induce oxidative stress in the hippocampus.[8,9,10,11] In summary, nicotine has been implicated in many significant physiologic processes, and it is likely that it may contribute to pathogenesis of disease in those who consume nicotine products.

Conversely, these findings do not imply that nicotine is completely without benefit. Aside from being required for proper functioning of the autonomic nervous system and other physiologies, endogenous nicotine has recently been shown to have beneficial effects as well. Nicotine may have significant neuroprotective features, especially in the pathogenesis of Parkinson's and Alzheimer's,[12,13,14] and may have a role in improving post-operative recovery when used in isolation.[15] Findings such as these have prompted careful reevaluation of potential harms and potential benefits of nicotine.

Addiction and The Gateway Hypothesis

The gateway hypothesis is a longstanding theory regarding the initiation of addiction and/or progression of drug-seeking behavior. Though the gateway hypothesis was initially developed as a result of observational epidemiological studies, recent findings have provided a molecular foundation for this hypothesis. In short, a potential mechanistic explanation has been developed to support the notion that an individual, following the use of tobacco cigarettes, may have an increased propensity for drug- seeking and/or addictive behavior.[16,17] Specifically, nicotine effectively primes the genome to widespread expression due to inhibition of histone deacetylase (HDAC).[16] Lower HDAC activity suggests greater acetylation of histones and thus allows increased transcription of a number of different genes. One such gene, *FoxB*, has been correlated with addictive and/or risk-taking behavior and may be transcriptionally upregulated through this mechanism.[17] Given these findings, the explosion of e-cigarette use accompanied by increased nicotine addiction among adolescents and young adults becomes even more concerning.

Nicotine on Cardiovascular Function

Nicotine and Hemodynamics

Nicotine increases neurotransmission in the brain and autonomic nervous system and causes release of norepinephrine from post-ganglionic sympathetic nerve terminals. The acute nicotine effects on the cardiovascular system largely reflect this sympathetic stimulation, including an abrupt increase in blood pressure, contractility, and heart rate following acute nicotine exposure.[4] The increases in heart rate and contractility largely lead to increases in cardiac output while peripheral effects can vary based on the location. To be specific, nicotine largely induces vasoconstriction in microvasculature peripherally but vasodilates in skeletal muscle vasculature.[18] The vasoconstriction may be harmful since limiting blood flow may

impair wound healing, placental blood flow, and kidney function.[19]

Furthermore, the effects of this nicotine-induced vasoconstriction may be particularly harmful in patients with microvascular-related diseases. For instance, diabetic patients with microvascular dysfunction are at risk for a number of sequelae including retinopathies, neuropathies, and nephropathies. In addition, it has long since been recognized that most of these outcomes are strongly correlated with chronic cigarette consumption.[19] Though not directly studied, nicotine itself could be a major constituent in the development of microvascular complications in diabetic patients due to its vasoconstrictive effects. If found to be true, clinical approaches to the diabetic smoker may need to be adjusted to extend beyond smoking cessation by incorporating measures to limit nicotine consumption. Further investigation in this field is necessary to determine the extent of nicotine's contribution to microvascular impairment.

Nicotine and Platelet Function

Historic experiments have shown that epinephrine is capable of inducing platelet aggregation through chloride-dependent mechanisms.[20] As a result, given nicotine's capacity to induce the release of epinephrine from the adrenal glands, there may be potential consequences for platelet function in the presence of nicotine exposure. Given the physiology, one would expect that nicotine exposure would promote platelet aggregation. However, numerous studies have come up with contradicting conclusions regarding *in vivo* effects.[21,22] In short, specific effects of nicotine on platelet function have yet to be ascertained.

Nicotine and Endothelial Function

In smokers, endothelial function is often disrupted and is believed to be one of the major initiating steps of atherosclerosis.[23] Typically, endothelial dysfunction seems to arise from inflammatory and/or oxidative stress on the vasculature, but some studies have suggested that nicotine in isolation can result in similar outcomes.[24] In one such study conducted on humans, direct intravenous infusion of nicotine at concentrations similar to that of a habitual smoker was sufficient in limiting nitrous oxide-mediated dilatory response to bradykinin.[24] These results imply that isolated nicotine, in the absence of combusted tobacco, may contribute to pathogenesis of atherosclerosis.

Nicotine and Inflammation

Historically, nicotine has been seen as an anti-inflammatory compound.[4,25] Despite this, there is evidence that nicotine may also possess harmful inflammatory properties as well. Specifically, in mouse models of atherosclerosis, an acute myocardial infarction activates the sympathetic nervous system, largely producing inflammation through stimulation of β3-adrenergic receptors. This inflammation accelerates the development of atherosclerosis. Nicotine, in having the capacity to activate the β3- andrenergic receptors, can mimic the effects seen in these models, and may contribute to atherogenesis in patients with previous myocardial infarction. Furthermore, other studies have shown that nicotine may have additional roles in promoting inflammation, such as increasing neutrophil chemotaxis and upregulation of toll-like receptors.[26,27] However, it is unclear what role these effects have on human physiology.

Nicotine and Lipid Metabolism

A small number of studies have found a role for nicotine in the development of dyslipidemia. Although atherogenic lipid profiles are more prevalent in experiments using cigarette smoke or oral tobacco, other studies using intravenous nicotine infusions demonstrated that nicotine in isolation decreased HDL and increased LDL and VLDL.[28,29,30] Though the mechanisms are unclear, it is proposed that nicotine can directly stimulate β3 receptors to induce lipolysis, increase free fatty acid concentrations, and thus, provide fuel for LDL production.[31]

In spite of this, nicotine-replacement cessation strategies seem to indicate that nicotine's role in altering lipid metabolism is likely less significant when compared to dyslipidemia induced by cigarette smoking. Former smokers using these therapies have shown positive changes in HDL/LDL ratios following adoption of alternative nicotine-containing products.[4] It remains to be seen how nicotine exposure in nicotine-naïve individual, such as a non-smoker who starts using e-cigarettes, may affect lipid profiles.

Other Potential Roles of Nicotine in Cardiovascular Disease

Additional findings have also supported the idea that nicotine may contribute to maladaptive structural changes in the heart. Evidence suggests that nicotine, through mechanisms of sympathetic activation can induce cardiomyocyte hypertrophy, and may contribute to pathogenesis of heart failure.[32]

Furthermore, nicotine may also have a role in the development of cardiac arrhythmias. Though arrhythmogenic effects have not been found in pharmacological studies of nicotine administered to humans, studies conducted in dogs suggest nicotine may induce transient sinus arrest/bradycardia, sinus tachycardia, atrial fibrillation, sinoatrial block, AV block, and ventricular tachyarrhythmia. Each of these rhythm abnormalities is thought to be somehow related to nicotine's ability to induce catecholamine release or interfere with inward rectifying potassium channels.[33]

Lastly, nicotine-induced vasoconstriction of the coronary arteries can induce ischemia and, when combined with subsequent catecholamine release, may produce the conditions necessary to precipitate myocardial infarction.[4]

Additional Caveats

The degree nicotine contributes to these adverse cardiovascular outcomes is difficult to ascertain. Human consumption of nicotine is most often accompanied by tobacco smoke, and as a result, establishing causality becomes problematic. To date,

findings from research on combustion-free nicotine products or other alternative delivery methods are often used to rule in or out potential contributions to disease or harm. For example, Swedish epidemiological studies regarding the use of snus and potential cardiovascular outcomes when compared to tobacco cigarette smokers determined that snus users had a lower risk of having myocardial infarctions or strokes.[34,35] Other studies, however, show that these smokeless products are not without harm, suggesting that their use is associated with an increase in cardiovascular disease in cigarette nonsmokers.[36] In either case, following a thorough review of the potential cardiovascular risks associated with smokeless tobacco use, the American Heart Association recommends that clinicians continue to discourage the use of these products.[37]

Clearly, these sorts of contradictions are particularly troublesome and exemplify some of the shortcomings of available nicotine-related research. However, given the general consensus that electronic cigarettes are safer than tobacco cigarettes and, in many circumstances, are recommended cessation strategies for tobacco smokers, determining the safety of nicotine exposure from these devices will soon become the crux of the matter.

Implications for Electronic Cigarettes

As of now, the findings of these nicotine studies are insufficient to implicate, or absolve, nicotine in causing significantly harmful disease processes. However, the growth in popularity of electronic cigarette use, in which the most prominent bioactive compound is aerosolized nicotine, is particularly alarming. With recent studies suggesting that a handful of the constituents within electronic cigarette aerosol may be harmful, it is plausible that long-term use of these products will manifest as a number of different diseases years from now. For these reasons, there is an explicit need for further research on nicotine, specifically aerosolized nicotine, and we as practitioners should be prepared for potential adverse consequences that may result from electronic cigarette use in the interim.

REFERENCES

1. **Lund I, Scheffels J.** The relative risk to health from snus and cigarettes: response to Grimsrud et al.'s commentary on "perceptions of the relative harmfulness of snus among Norwegian general practitioners and their effect on the tendency to recommend snus in smoking cessation". *Nicotine Tob Res*. 2013 Jan;15(1):304-5. doi: 10.1093/ntr/nts190. PubMed PMID: 22990229; PubMed Central PMCID: PMC3524071.
2. **Øverland S, Skogen JC, Lissner L, Bjerkeset O, Tjora T, Stewart R.** Snus use and cardiovascular risk factors in the general population: the HUNT3 study. *Addiction*. 2013 Nov;108(11):2019-28. doi: 10.1111/add.12313. PubMed PMID:23909909.
3. **McAuley TR, Hopke PK, Zhao J, Babaian S**. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. *Inhal Toxicol*. 2012 Oct;24(12):850-7. doi: 10.3109/08958378.2012.724728. PubMed PMID: 23033998.
4. **Benowitz NL, Burbank AD.** Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. *Trends Cardiovasc Med*. 2016 Aug;26(6):515-23. doi: 10.1016/j.tcm.2016.03.001. Review. PubMed PMID: 27079891; PubMed Central PMCID: PMC4958544.
5. **Lavelle C, Birek C, Scott DA**. Are nicotine replacement strategies to facilitate smoking cessation safe? *J Can Dent Assoc*. 2003 Oct;69(9):592-7. Review. PubMed PMID: 14653935.
6. **Bodas M, Van Westphal C, Carpenter-Thompson R, K Mohanty D, Vij N**. Nicotine exposure induces bronchial epithelial cell apoptosis and senescence via ROS mediated autophagy-impairment. *Free Radic Biol Med*. 2016 Aug;97:441-53. doi:10.1016/j.freeradbiomed.2016.06.017. PubMed PMID: 27394171.
7. **Zhang C, Ding XP, Zhao QN, Yang XJ, An SM, Wang H, Xu L, Zhu L, Chen HZ.** Role of a7-nicotinic acetylcholine receptor in nicotine-induced invasion and epithelial-to-mesenchymal transition in human non-small cell lung cancer cells. *Oncotarget*. 2016 Jul 8. doi: 10.18632/oncotarget.10498. [Epub ahead of print] PubMed PMID: 27409670.
8. **Jarvis MJ, Russell MA, Benowitz NL, Feyerabend C.** Elimination of cotinine from body fluids: implications for noninvasive measurement of tobacco smoke exposure. *Am J Public Health*. 1988 Jun;78(6):696-8. PubMed PMID: 3369603; PubMed Central PMCID: PMC1350287.
9. **de Aguiar RB, Parfitt GM, Jaboinski J, Barros DM**. Neuroactive effects of cotinine on the hippocampus: behavioral and biochemical parameters. *Neuropharmacology*. 2013 Aug;71:292-8. doi: 10.1016/j.neuropharm.2013.03.032. PubMed PMID: 23602986.
10. **Dalgic A, Okay O, Helvacioglu F, Daglioglu E, Akdag R, Take G, Belen D.** Tobacco-induced neuronal degeneration via cotinine in rats subjected to experimental spinal cord injury. *J Neurol Surg A Cent Eur Neurosurg*. 2013 May;74(3):136-45. doi: 10.1055/s-0033-1337607. PubMed PMID: 23512588.
11. **Jacob T, Clouden N, Hingorani A, Ascher E.** The effect of cotinine on telomerase activity in human vascular smooth muscle cells. *J Cardiovasc Surg (Torino).* 2009 Jun;50(3):345-9. PubMed PMID: 19339962.
12. **Xue MQ, Liu XX, Zhang YL, Gao FG.** Nicotine exerts neuroprotective effects against β-amyloid-induced neurotoxicity in SH-SY5Y cells through the Erk1/2-p38-JNK-dependent signaling pathway. *Int J Mol Med*. 2014 Apr;33(4):925-33. doi: 10.3892/ijmm.2014.1632. PubMed PMID: 24481039.
13. **Gao J, Adam BL, Terry AV Jr**. Evaluation of nicotine and cotinine analogs as potential neuroprotective agents for Alzheimer's disease. *Bioorg Med Chem Lett*. 2014 Mar 15;24(6):1472-8. doi: 10.1016/j.bmcl.2014.02.008. PubMed PMID: 24581918; PubMed Central PMCID: PMC4027973.

14. **Quik M, Perez XA, Bordia T.** Nicotine as a potential neuroprotective agent for Parkinson's disease. *Mov Disord*. 2012 Jul;27(8):947-57. doi: 10.1002/mds.25028. Review. PubMed PMID: 22693036; PubMed Central PMCID: PMC3685410.
15. **Reuther WJ, Brennan PA.** Is nicotine still the bad guy? Summary of the effects of smoking on patients with head and neck cancer in the postoperative period and the uses of nicotine replacement therapy in these patients. *Br J Oral Maxillofac Surg*. 2014 Feb;52(2):102-5. doi: 10.1016/j.bjoms.2013.11.003. Review. PubMed PMID: 24315200.
16. **Kandel ER, Kandel DB.** Shattuck Lecture. A molecular basis for nicotine as a gateway drug. *N Engl J Med*. 2014 Sep 4;371(10):932-43. doi:10.1056/NEJMsa1405092. PubMed PMID: 25184865; PubMed Central PMCID: PMC4353486.
17. **Nestler EJ, Barrot M, Self DW.** DeltaFosB: a sustained molecular switch for addiction. *Proc Natl Acad Sci U S A*. 2001 Sep 25;98(20):11042-6. Review. PubMed PMID: 11572966; PubMed Central PMCID: PMC58680.
18. **Diana JN, Qian SF, Heesch CM, Barron KW, Chien CY.** Nicotine-induced skeletal muscle vasodilation is mediated by release of epinephrine from nerve terminals. *Am J Physiol*. 1990 Dec;259(6 Pt 2):H1718-29. PubMed PMID: 1979721.
19. **Chakkarwar VA.** Smoking in diabetic nephropathy: sparks in the fuel tank? *World J Diabetes*. 2012 Dec 15;3(12):186-95. doi: 10.4239/wjd.v3.i12.186. PubMed PMID: 23301120; PubMed Central PMCID: PMC3538984.
20. **Spalding A, Vaitkevicius H, Dill S, MacKenzie S, Schmaier A, Lockette W**. Mechanism of epinephrine-induced platelet aggregation. *Hypertension*. 1998 Feb;31(2):603-7. PubMed PMID: 9461228.
21. **Hom S, Chen L, Wang T, Ghebrehiwet B, Yin W, Rubenstein DA.** Platelet activation, adhesion, inflammation, and aggregation potential are altered in the presence of electronic cigarette extracts of variable nicotine concentrations. *Platelets*. 2016 Apr 20:1-9. [Epub ahead of print] PubMed PMID: 27096416.
22. **Girdhar G, Xu S, Bluestein D, Jesty J**. Reduced-nicotine cigarettes increase platelet activation in smokers in vivo: a dilemma in harm reduction. *Nicotine Tob Res*. 2008 Dec;10(12):1737-44. doi: 10.1080/14622200802443528. PubMed PMID:18982536.
23. **Messner B, Bernhard D.** Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. *Arterioscler Thromb Vasc Biol*. 2014 Mar;34(3):509-15. doi: 10.1161/ATVBAHA.113.300156. Review. PubMed PMID: 24554606.
24. **Chalon S, Moreno H Jr, Benowitz NL, Hoffman BB, Blaschke TF.** Nicotine impairs endothelium-dependent dilatation in human veins in vivo. *Clin Pharmacol Ther*. 2000 Apr;67(4):391-7. PubMed PMID: 10801248.
25. **Zdanowski R, Krzyżowska M, Ujazdowska D, Lewicka A, Lewicki S.** Role of α7 nicotinic receptor in the immune system and intracellular signaling pathways. *Cent Eur J Immunol*. 2015;40(3):373-9. doi: 10.5114/ceji.2015.54602. Review. PubMed PMID: 26648784; PubMed Central PMCID: PMC4655390.
26. **Nowak D, Ruta U, Piasecka G.** Nicotine increases human polymorphonuclear leukocytes chemotactic response--a possible additional mechanism of lung injury in cigarette smokers. *Exp Pathol*. 1990;39(1):37-43. PubMed PMID: 2394238.
27. **Xu Y, Zhang Y, Cardell LO**. Nicotine exaggerates LPS-induced airway hyperreactivity via JNK-mediated up-regulation of Toll-like receptor 4. *Am J Respir Cell Mol Biol*. 2014 Sep;51(3):370-9. doi: 10.1165/rcmb.2013-0409OC. PubMed PMID: 24669857.
28. **Cluette-Brown J, Mulligan J, Doyle K, Hagan S, Osmolski T, Hojnacki J**. Oral nicotine induces an atherogenic lipoprotein profile. *Proc Soc Exp Biol Med*. 1986 Jul;182(3):409-13. PubMed PMID: 3714724.
29. **Latha MS, Vijayammal PL, Kurup PA.** Effect of nicotine administration on lipid metabolism in rats. *Indian J Med Re*s. 1993 Feb;98:44-9. PubMed PMID: 8495991.
30. **Quensel M, Agardh CD, Nilsson-Ehle P.** Nicotine does not affect plasma lipoprotein concentrations in healthy men. *Scand J Clin Lab Invest*. 1989 Apr;49(2):149-53. PubMed PMID: 2520366.
31. **Andersson K, Arner P**. Systemic nicotine stimulates human adipose tissue lipolysis through local cholinergic and catecholaminergic receptors. *Int J Obes Relat Metab Disord*. 2001 Aug;25(8):1225-32. PubMed PMID: 11477508.
32. **Li N, Si B, Ju JF, Zhu M, You F, Wang D, Ren J, Ning YS, Zhang FQ, Dong K, Huang J, Yu WQ, Wang TJ, Qiao B**. Nicotine Induces Cardiomyocyte Hypertrophy Through TRPC3-Mediated Ca(2+)/NFAT Signalling Pathway. *Can J Cardiol*. 2016 Oct;32(10):1260.e1-1260.e10. doi: 10.1016/j.cjca.2015.12.015. PubMed PMID:26952156.
33. **D'Alessandro A, Boeckelmann I, Hammwhöner M, Goette A**. Nicotine, cigarette smoking and cardiac arrhythmia: an overview. *Eur J Prev Cardiol*. 2012 Jun;19(3):297-305. Review. PubMed PMID: 22779085.
34. **Hansson J, Galanti MR, Hergens MP, Fredlund P, Ahlbom A, Alfredsson L, Bellocco R, Eriksson M, Hallqvist J, Hedblad B, Jansson JH, Nilsson P, Pedersen N, Trolle Lagerros Y, Ostergren PO, Magnusson C**. Use of snus and acute myocardial infarction: pooled analysis of eight prospective observational studies. *Eur J Epidemiol*. 2012 Oct;27(10):771-9. doi: 10.1007/s10654-012-9704-8. PubMed PMID: 22722951.
35. **Hansson J, Galanti MR, Hergens MP, Fredlund P, Ahlbom A, Alfredsson L, Bellocco R, Engström G, Eriksson M, Hallqvist J, Hedblad B, Jansson JH, Pedersen NL, Trolle Lagerros Y, Ostergren PO, Magnusson C.** Snus (Swedish smokeless tobacco) use and risk of stroke: pooled analyses of incidence and survival. *J Intern Med*. 2014 Jul;276(1):87-95. doi: 10.1111/joim.12219. PubMed PMID: 24548296.
36. **Yatsuya H, Folsom AR; ARIC Investigators.** Risk of incident cardiovascular disease among users of smokeless tobacco in the Atherosclerosis Risk in Communities

(ARIC) study. *Am J Epidemiol*. 2010 Sep 1;172(5):600-5. doi: 10.1093/aje/kwq191. PubMed PMID: 20688904; PubMed Central PMCID: PMC2950823.

37. **Piano MR, Benowitz NL, Fitzgerald GA, Corbridge S, Heath J, Hahn E, Pechacek TF, Howard G; American Heart Association Council on Cardiovascular Nursing.** Impact of smokeless tobacco products on cardiovascular disease: implications for policy, prevention, and treatment: a policy statement from the American Heart Association. *Circulation*. 2010 Oct 12;122(15):1520-44. doi:10.1161/CIR.0b013e3181f432c3. PubMed PMID: 20837898.

Submitted September 23, 2016