Electronic cigarettes and nicotine dependence: evolving products, evolving problems

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Abstract

Electronic cigarettes (ECIGs) use an electric heater to aerosolize a liquid that usually contains propylene glycol, vegetable glycerin, flavorants, and the dependence-producing drug nicotine. ECIG-induced nicotine dependence has become an important concern, as some ECIGs deliver very little nicotine while some may exceed the nicotine delivery profile of a tobacco cigarette. This variability is relevant to tobacco cigarette smokers who try to switch to ECIGs. Products with very low nicotine delivery may not substitute for tobacco cigarettes, so that ECIG use is accompanied by little reduced risk of cigarette-caused disease. Products with very high nicotine delivery may make quitting ECIGs particularly difficult should users decide to try. For non-smokers, the wide variability of ECIGs on the market is especially troublesome: low nicotine products may lead them to initiate nicotine self-administration and progress to higher dosing ECIGs or other products, and those that deliver more nicotine may produce nicotine dependence where it was not otherwise present. External regulatory action, guided by strong science, may be required to ensure that population-level nicotine dependence does not rise.

Keywords: Dependence, Electronic cigarettes, Nicotine, Non-smokers, Smokers

Background

Electronic cigarettes (ECIGs) use an electric heater to aerosolize a liquid that usually contains some combination of propylene glycol, vegetable glycerin, flavorants, and nicotine. Nicotine is a mild psychomotor stimulant that supports repeated self-administration as well as the development of drug dependence, a neurobiological adaptation to repeated drug exposure that is manifested behaviorally by compulsive drug self-administration, an aversive withdrawal syndrome upon cessation, and an inability to quit despite a desire to do so and repeated cessation attempts [1,2]. There is an ongoing and lively debate regarding the potential for ECIGs to influence individual and public health for better [3,4] or for worse [5-7]. This debate frequently highlights the effects that ECIGs may have on cigarette smoking cessation and initiation, and in those contexts has touched on the impact of ECIGs on maintaining nicotine dependence where it already exists (i.e., in current cigarette smokers) or developing it where it does not (i.e., in never smokers or former smokers). The issue of ECIGs and nicotine dependence has become increasingly important in line with the rapid development of nicotine delivery methods, with earlier models largely being ineffective [8,9], and later models delivering nicotine to the user’s bloodstream much in the same manner as the tobacco cigarette [10] – a product optimally designed to increase the likelihood of chronic use or dependence [11]. If this evolution continues, ECIGs with a nicotine delivery profile that exceeds that of a tobacco cigarette may soon be commonplace [12]. The availability of such products may have profound effects for people who currently smoke tobacco cigarettes, as well as those who do not.

Current smokers

For current tobacco cigarette smokers much has been written about the potential benefits of ECIGs [13,14]. These individuals are almost certainly already dependent on cigarette-delivered nicotine, and self-administer it via toxicant-laden tobacco smoke that causes a variety of lethal disorders including cancer, cardiovascular disease, and pulmonary disease [11]. The potential benefit of ECIGs for this population is that nicotine can be self-administered in an aerosol that contains far fewer
Current non-smokers

Non-smokers include never smokers and former smokers, few of whom currently are nicotine dependent. These individuals are already at risk for ECIG-initiated nicotine dependence due to marketing methods that may target them [24,25], nicotine-containing liquids that mimic the flavors of highly palatable foods and drinks [25,26], and relatively unrestricted ECIG access [27]. Survey data suggest that at least some non-smokers are already experimenting with ECIGs [28-31]. The extent to which this experimentation will become compulsive use is unclear. If it does, all of the arguments above become more compelling. In addition to the risks associated with ECIGs that deliver nicotine at a rate above a tobacco cigarette, ECIGs that deliver low levels of nicotine may function as the so-called ‘starter products’ common in the smokeless tobacco arena [32]. These starter products allow nicotine-naïve users to self-administer low doses of nicotine without experiencing drug-mediated adverse side effects, and then, as tolerance develops, they can ‘graduate’ to products that deliver increasing doses of the drug [32]. Thus, ECIGs that deliver little nicotine might start nicotine-naïve users on the trajectory to compulsive nicotine use, whereas products that deliver even more nicotine than a tobacco cigarette have the potential to make ECIG cessation even more difficult than smoking cessation. A similar line of reasoning follows for former smokers, who not only risk a return to nicotine dependence via ECIGs, but also the possibility of relapse to their previously-preferred nicotine self-administration method, the lethal tobacco cigarette. If ECIG producers are unwilling to act so that their products do not lead never-smokers and former smokers into compulsive nicotine use, empirically-based ECIG regulation may have an important role to play in avoiding this outcome.

Conclusions

The evolution of the ECIG from a class of products that failed to deliver nicotine to one that has the potential to exceed the nicotine delivery of a tobacco cigarette is a concern for all. This concern is not based on some ideological or moral position regarding drug dependence [4], but rather on an understanding of the financial, behavioral, and social ramifications of compulsive drug use. As others have suggested [4,13,14], ECIG use well may be a method for achieving significant decreases in the disability, disease, and death associated with combustible tobacco use worldwide. Achieving these decreases may require ECIGs that approach the nicotine delivery profile of a tobacco cigarette, but likely do not require ECIGs that exceed that profile. In addition, these decreases in cigarette-caused morbidity and mortality must not be accompanied by an increase in compulsive nicotine use.
among those who do not currently use the drug. A profit-minded ECIg industry may require external regulatory force, guided by strong science, to ensure that population-level nicotine dependence does not rise. Relevant targets for further research and potential regulatory intervention include product characteristics [33] and nicotine flux [34,35], as well as product advertising and access [36]. In addition, this discussion has focused exclusively on nicotine; regulation can also limit user exposure to other ECIg toxicants, including those contained in the liquid [37,38] as well as those produced when the liquid is heated [37,39,40].

Competing interests
The authors declare that they have no competing interest.

Authors’ information
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References
1. US Department of Health and Human Services. The health consequences of smoking: nicotine addiction. A report of the surgeon general. Atlanta (GA): US Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 1988. p. 88–8406. DHHS Publication No. (CDC).
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: APA; 2013.
3. Ettter JF. Should electronic cigarettes be as freely available as tobacco? Yes. BMJ 2013;346:F3845.
4. Hajek P. Electronic cigarettes have a potential for huge public health benefit. BMC Med. 2014;12:225.
5. Chapman S. Should electronic cigarettes be as freely available as tobacco cigarettes? No. BMJ. 2013;346:F3840.
6. Mazik W. Harm reduction at the crossroads: the case of e-cigarettes. Am J Prev Med. 2014;47:505–7.
7. Pisinger C. Why public health people are more worried than excited over e-cigarettes. BMC Med. 2014;12:226.
8. Vansickel AR, Cobb CO, Weaver MF, Eisenberg T. A clinical laboratory model for evaluating the acute effects of electronic “cigarettes”: nicotine delivery profile and cardiovascular and subjective effects. Cancer Epidemiol Biomarkers Prev. 2010;19:1945–53.
9. Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomized cross-over trial. Tob Control. 2010;19:98–103.
10. Spindle T, Breland A, Kaoaoghlian N, Shihadeh AL, Eisenberg T. Preliminary results of an examination of electronic cigarette user puff topography. The effect of a mouthpiece-based topography measurement device on plasma nicotine and subjective effects. Nicotine Tob Res. 2015;17:142–9.
11. US Department of Health and Human Services. The health consequences of smoking—50 years of progress. A Report of the Surgeon General. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
12. Hiler M, Kilgallen B, Breland A, Lipato T, Eisenberg T. Is an electronic cigarette user’s plasma nicotine concentration related to liquid nicotine concentration? Poster presented at the 21st annual meeting of the Society for Research on Nicotine and Tobacco, Philadelphia, PA. 2015. https://www.sirt.org/conferences/SRT_2015_Abstracts_WEB.pdf. Accessed 1 April 2015.
13. Polosa R, Rodu B, Caponnetto P, Maglia M, Raccì C. A fresh look at tobacco harm reduction: the case for the electronic cigarette. Harm Reduct J. 2013;10:19.
14. Abrams DB. Promise and peril of e-cigarettes: can disruptive technology make cigarettes obsolete? JAMA. 2014;311:135–6.
15. Goniewicz ML, Kiyak J, Gawron M, Kosiader S, Sobczak A, Kurek J, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tob Control. 2014;23:133–9.
16. Pisinger C, Godtfredsen NS. Is there a health benefit of reduced tobacco consumption? A systematic review. Nicotine Tob Res. 2007;9:631–46.
17. Bjaervell K, Tverdal A. Health consequences of smoking 1-4 cigarettes per day: response to GF Cope (e-letter to journal). Tob Control. 2006:15:71–2.
18. Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, et al. Electronic cigarettes for smoking cessation: a randomized controlled trial. Lancet. 2013;382:1629–37.
19. Ko CH, Yen JY, Yen CF, Chen CS, Chen CC. The association between Internet addiction and psychiatric disorder: a review of the literature. Eur Psychiatry. 2012;27:1–8.
20. Reuter J, Raedler T, Rose M, Hand J, Glässer J, Büchel C. Pathological gambling is linked to reduced activation of the mesolimbic reward system. Nat Neurosci. 2005;8:147–8.
21. Lorenz RC, Krüger J, Neumann B, Schott BH, Kaufmann C, Heinz A, et al. Cue reactivity and its inhibition in pathological computer game players. Addict Biol. 2013;18:134–46.
22. Ettter JF, Eisenberg T. Dependence levels in users of electronic cigarettes, nicotine gummies and tobacco cigarettes. Drug Alcohol Depend. 2015;147:68–75.
23. Foulds J, Veldheer S, Yingst J, Habrovsky S, Wilson SJ, Nichols TT, et al. Development of a questionnaire for assessing dependence on electronic cigarettes among a large sample of ex-smoking E-cigarette users. Nicotine Tob Res. 2015;17:186–92.
24. Richardson A, Ganz O, Vallone D. Tobacco on the web: surveillance and characterisation of online tobacco and e-cigarette advertising. Tob Control. 2014. Ahead of print.
25. Grana RA, Ling PM. ‘Smoking revolution’: a content analysis of electronic cigarette retail websites. Am J Prev Med. 2014;46:395–403.
26. Zhu SH, Sun JY, Bonnevie E, Cummins SE, Gamst A, Yin L, et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. Tob Control. 2014;23 Suppl 3:iii3–9.
27. Gourdet CK, Chriqui JF, Chaloupka FJ. A baseline understanding of state laws governing e-cigarettes. Tob Control. 2014;23:iii37–40.
28. Bunnell RE, Agaku IT, Arrazola RA, Apelberg BJ, Caraballo RS, Corey CG, et al. Intentions to smoke cigarettes among never-smoking US middle and high school electronic cigarette users: National Youth Tobacco Survey, 2011–2013. Nicotine Tob Res. 2015;17:228.
29. King BA, Patel R, Nguyen KH, Dube SR. Trends in awareness and use of electronic cigarettes among US adults, 2010–2013. Nicotine Tob Res. 2015;17:219–27.
30. Dockrell M, Morrison R, Bauld L, McNeill A. E-cigarettes: prevalence and attitudes in Great Britain. Nicotine Tob Res. 2013;15:1737–44.
31. Li J, Newcombe R, Walton D. The prevalence, correlates and reasons for using electronic cigarettes among New Zealand adults. Addict Behav. 2015;45:245–51.
32. Connolly GN. The marketing of nicotine addiction by one oral snuff manufacturer. Tob Control. 1995;4:73–9.
33. Talih S, Balhas Z, Eisenberg T, Salman R, Karamghalian N, El Hellani A, et al. Effects of user puff topography, device voltage, and liquid nicotine concentration on electronic cigarette nicotine yield: measurements and model predictions. Nicotine Tob Res. 2015;17:150–7.
34. Shihadeh A, Eisenberg T. Electronic cigarette effectiveness and abuse liability: Predicting and regulating ‘nicotine flux’. Nicotine Tob Res. 2015;17:59–62.
35. Eisenberg T, Shihadeh A. Nicotine flux: a potentially important tool for regulating electronic cigarettes. Nicotine Tob Res. 2015;17:165–7.
36. Lindblom EN. Effectively regulating e-cigarettes and their advertising-and the first amendment. Food Drug Law J. 2015;70:57–94.
37. Farsalinos KE, Kistler KA, Gillman G, Voudris V. Evaluation of electronic cigarette liquids and aerosol for the presence of selected inhalation toxins. Nicotine Tob Res. 2015;17:168–74.
38. Wu Q, Jiang D, Minor M, Chu HW. Electronic cigarette liquid increases inflammation and virus infection in primary human airway epithelial cells. PLoS One. 2014;9, e108342.
39. Bekki K, Uchiyama S, Ohta K, Inaba Y, Nakagome H, Kunugita N. Carbonyl compounds generated from electronic cigarettes. Int J Environ Res Public Health. 2014;11:192–200.
40. Lerner CA, Sundar IK, Yao H, Gerloff J, Ossip DJ, McIntosh S, et al. Vapors produced by electronic cigarettes and e-juices with flavorings induce toxicity, oxidative stress, and inflammatory response in lung epithelial cells and in mouse lung. PLoS One. 2015;10, e0116732.

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