

**November 2021:** NICE guidelines PH45 (June 2013) PH48 (November 2013) have been updated and replaced by NG209.

The recommendations labelled [2013] or [2013, amended 2021] in the updated guideline were based on these evidence reviews.

See [www.nice.org.uk/guidance/NG209](http://www.nice.org.uk/guidance/NG209) for all the current recommendations and evidence reviews.

Expert paper 1: Electronic cigarettes - nicotine delivery, efficacy in smoking cessation and potential for harm reduction - expert paper by Maciej Goniewicz

## Electronic cigarettes

**Nicotine delivery, efficacy in smoking cessation, and potential for harm reduction. Review.**

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### Background

Electronic nicotine delivery systems (ENDS), called **electronic cigarettes** or **e-cigarettes**, are battery-powered devices that deliver a vaporized liquid nicotine solution, usually in propylene glycol. In addition to nicotine delivery, the vapour also provides a flavour and physical sensation similar to that of inhaled tobacco smoke, while no tobacco, smoke, or combustion is actually involved in its operation.

There is currently a growing interest in e-cigarettes for several reasons:

*E-cigarettes may have a potential to impact public health.* The best solution for smokers to avoid health risk associated with cigarettes is to stop smoking. However, many are unable to do so. For such smokers, harm reduction strategies are increasingly seen as an important alternative which could deliver substantial reductions in the mortality and morbidity currently caused by tobacco. The substitution of tobacco smoking with a safer alternative is one such option. A scenario where a safer nicotine delivery consumer product replaces cigarettes is an attractive one. If products such as e-cigarettes were proven to be less hazardous than tobacco smoking and provided an acceptable substitute to conventional cigarettes for smokers who cannot or do not want to stop smoking, this could generate a substantial public health benefit. First however a number of questions need to be answered about whether e-cigarettes poses new health problems or serves as a gateway to smoking conventional cigarettes, and whether it is actually attractive enough for smokers to replace conventional cigarettes and to provide any harm reductions benefits.

*E-cigarettes may have a potential in smoking cessation.* Current stop-smoking treatments have limited efficacy. The NHS Stop Smoking Service (NHS-SSS) uses a state-of-the-art combination of medicines and behavioral support, but neither of these approaches targets the habit and sensory input that smokers miss when they stop smoking. The e-cigarettes may potentially act as a behavioural replacement for smoking and it can also provide nicotine at levels that are at least on par with those provided by pharmaceutical nicotine replacement products. It may thus have a potential to complement and enhance existing treatments. This at least seems to be the opinion of a number of smokers. The NHS-SSS advisors increasingly encounter smokers who see e-cigarette as a potential tool which may help them to stop smoking. They are asked for advice and they seek guidance on what to tell smokers about e-cigarettes. The MHRA recently instigated public consultation on legal status of e-cigarettes. Evidence is needed on e-cigarette safety and efficacy when used to assist in smoking cessation.

### ***What is known about e-cigarettes?***

#### *Nicotine delivery*

Regarding nicotine delivery, not all brands of e-cigarette deliver nicotine and those which provide nicotine do so with different efficacy (Eissenberg et al, 2010; Vansickel et al, 2010). Some brands deliver nicotine more effectively than the existing oral NRT products (Goniewicz et al, 2012a).

I conducted the study to analyze nicotine levels in vapor generated from various e-cigarette brands (Goniewicz et al, 2012a). The study was designed to assess efficacy and consistency of various e-cigarette brands in converting nicotine to vapor and to analyze dynamics of nicotine vaporization. Sixteen e-cigarette brands were selected based on their popularity in the Polish, UK and US markets. Vapors were generated using an automatic smoking-machine modified to simulate puffing conditions of real e-cigarette users. Nicotine was absorbed in a set of washing-bottles with methanol and analyzed with gas chromatography. Results showed that total level of nicotine in vapor generated by 20 series of 15 puffs varied from 0.5 to 15.4 mg. Most of the analyzed e-cigarettes effectively delivered nicotine during the first 150-180 puffs. On average 50-60% of nicotine from a cartridge was vaporized. I concluded that e-cigarettes generate vapor that contains nicotine, but EC brands differ in their efficacy and consistency of nicotine vaporization. If the e-cigarette is effective in vaporizing nicotine, the amount inhaled from 15 puffs is lower compared with smoking a conventional cigarette.

Substantial amounts of cotinine (nicotine metabolite) were found in the saliva of e-cigarette users (Etter, 2011). The cotinine levels in e-cigarette users were similar to levels observed in smokers and higher than levels usually observed in NRT users. This finding has important implications for e-cigarette use by smokers who want to quit, for future research, and for the regulation of these products.

#### *Toxicants in e-cigarettes*

Preliminary studies found traces of selected tobacco-specific toxicants in some products, but in amounts much lower than in conventional cigarettes with clinically associated danger being probably very low (US FDA, Westenberger, 2009; Laugesen, 2008, 2009). More data on toxicants accumulation in longer-term users are needed.

The aim of my study was to evaluate changes in nicotine delivery and selected toxicant exposure after switching from tobacco cigarettes to e-cigarettes among 20 cigarette smokers (Goniewicz et al, 2012b). Subjects were provided with e-cigarettes with cartridges containing 16mg of nicotine and were asked to substitute their regular tobacco cigarettes with e-cigarettes for 2 weeks. Subjects provided urine samples at the day of switching (baseline) and after one and two weeks of using e-cigarettes. I analyzed urine for nicotine metabolites, NNAL (metabolite of tobacco-specific carcinogenic nitrosamine NNK), and hydroxyalkyl mercapturic acids (HAMAs, the main urinary metabolites of several alkylating substances that possess a carcinogenic potential). All subjects reported significant reduction of tobacco cigarettes smoked during the study; CPD decreased from 16.2 (95%CI 13.8; 18.5) to 0.6 (95%CI -1.7; 3.0,  $p < 0.05$ ) and exhaled CO decreased from 15.6 (95%CI 7.4; 23.8) to 4.2 ppm (95%CI 2.4; 5.9,  $p < 0.05$ ) after two weeks of using e-cigarettes. There were no significant changes in urine total nicotine metabolites (50.0 (95%CI 37.2; 62.9) vs. 44.7 nmol/mg creatinine (95%CI 25.2; 64.2),  $p = 0.89$ ). Urine levels of NNAL decreased by 64% from 225 (95%CI 148; 303) to 80 pmol/mg creatinine (95%CI 48; 112),  $p < 0.05$ . The average reductions in HAMAs varied

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from 54% (metabolite of propylene oxide) to 89% (metabolite of 1,3-butadiene),  $p < 0.05$ . I concluded that after switching from tobacco to electronic cigarettes nicotine exposure is unchanged while exposure to selected toxicants is substantially reduced. Further research is needed to evaluate long term effects of switching, including the health effects of continued use of e-cigarettes.

### *Effect of e-cigarettes on cigarette consumption and urges to smoke*

E-cigarettes can alleviate urges to smoke (Bullen et al, 2010; Vansickel et al, 2010), though a brand delivering no nicotine has no effect (Eisenberg, 2010). One study allowed a pilot comparison of e-cigarette and inhalator though its main objective was a comparison of e-cigarette with and without nicotine. Puffing for 20 minutes on the inhalator and puffing for 5 minutes on e-cigarette had similar effects on desire to smoke after overnight abstinence (Bullen et al. 2011).

Several internet surveys reported that e-cigarette users consider the product a satisfactory replacement for cigarettes and an effective stop-smoking treatment. They typically located e-cigarette brands with good nicotine delivery. In all surveys users mostly stopped smoking or substantially reduced their smoke intake (Etter, 2010; Siegel et al, 2011; Etter et al, 2011). This needs to be interpreted with caution as such surveys are more likely to attract e-cigarette enthusiasts rather than users who found the product disappointing.

I conducted the study to investigate patterns and effects of e-cigarette use and user beliefs about e-cigarette safety and benefits (Goniewicz et al, 2012c). E-cigarette users in Poland were recruited online and asked to participate in a web-based survey. The participants provided information on their smoking history, patterns of e-cigarette use, beliefs and attitudes regarding the product, and information on concurrent use of conventional cigarettes. The survey was completed by 179 e-cigarette users. Almost all participants used e-cigarette daily. E-cigarette was used primarily to quit smoking or to reduce harm associated with smoking (both 41%), and it was remarkably successful in helping the users to achieve these goals with 66% not smoking conventional cigarettes at all and 25% smoking under 5 cigarettes a day. Most participants (82%) thought that e-cigarettes are not totally safe, but that they are less dangerous than conventional cigarettes. 60% believed that e-cigarettes are addictive, but less so than conventional cigarettes. 54% perceived themselves as addicted to e-cigarette.

One study prospectively monitored possible modifications in smoking habits among 40 regular smokers unwilling to quit experimenting e-cigarette (Polosa et al. 2011). Study participants were invited to attend a total of five study visits over 6 months. Product use, number of cigarettes smoked, and exhaled carbon monoxide levels were measured at each visit. The study found that use of e-cigarette substantially decreased cigarette consumption without causing significant side effects in participants. Sustained 50% reduction in the number of cig/day after 24 weeks was shown in 13/40 (32.5%) participants; their median of 25 cigs/day decreasing to 6 cigs/day ( $p < 0.001$ ). Sustained smoking abstinence at week-24 was observed in 9/40 (22.5%) participants, with 6/9 still using the e-cigarette by the end of the study.

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## Expert paper 1: Electronic cigarettes - nicotine delivery, efficacy in smoking cessation and potential for harm reduction - expert paper by Maciej Goniewicz

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