

CORONARY ARTERY DISEASE PREVENTION & THERAPY UPDATE

Electronic Cigarette: Bridge to Quitting & Not a Substitute!

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KEY WORDS: *vaping; smoking
cessation*

ABBREVIATIONS

CI = confidence intervals
NRT = nicotine replacement therapy
TSNA = tobacco specific N-nitrosamines

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INTRODUCTION

Smoking is the leading cause of preventable death in the world and hence significant effort is made in order to promote, assist and maintain smoking cessation. Several methods have been recruited to this cause. Behavioral therapy had a relatively modest effect.¹ Drug interventions used nicotine replacement therapy (NRT) which reduces the symptoms of nicotine withdrawal, anti-depressant therapy with bupropion (marketed by GlaxoSmithKline as *Zyban* and other names), a weak dopamine and norepinephrine reuptake inhibitor to counteract depression caused by smoking cessation, and varenicline (trade name *Chantix* in the USA and *Champix* in Europe, marketed by Pfizer) which is a nicotinic acetylcholine receptor partial agonist. Its mechanism of action is considered to be stimulating release of dopamine to reduce craving and withdrawal and at the same time blocking the full spectrum of neurobiological effects of smoked nicotine.²⁻⁴ Data from meta-analyses show odds ratios for smoking cessation ranging from 1.6 for bupropion to 2.96 for varenicline, always in favor of the intervention, in 12 months.⁵ However, despite the effectiveness of these therapies, rates of smoking remain high at one year in the treatment groups and the development of novel methods is warranted.⁶

ELECTRONIC CIGARETTE

Electronic cigarette (e-cigarette) has been marketed as a smokeless alternative to conventional cigarette, cheaper and safer, and as a potential cessation method and it gained significant popularity quickly. Sales from the e-cigarette market doubled from \$250 to \$500 million between 2011 and 2012, and are expected to quadruple by 2014.⁷ However, certain legal issues have arisen since e-cigarettes contain nitrosamines, diethylene glycol, and other potentially harmful substances.⁸ The Food and Drug Administration in the US suggested that the sale of e-cigarettes should be prohibited or regulated as dangerous nicotine delivery systems and the US Court of Appeals decided that e-cigarettes may not be marketed as a safer alternative to cigarettes, or as a smoking cessation device, but instead must be sold as a smokeless tobacco product subject to the same rules and regulations of other tobacco products.^{9,10}

The chemical analysis of the solution and vapor of e-cigarettes, which represents the potential perils from extended use, is also controversial. In most of the studies their ingredients are non-toxic and non-carcinogenic, especially in the low quantities delivered. They include nicotine, propylene glycol, glycerin, and tobacco flavoring. A small amount of diethylene glycol (approximately 1%), a known carcinogen and an

ingredient in anti-freeze, has also been detected.¹¹ It is useful to note that smoke of traditional cigarettes contains thousands of compounds, such as heavy metals (cadmium, arsenic, chromium, nickel, and lead), tobacco specific N-nitrosamines (TSNA), polycyclic aromatic hydrocarbons and volatile organic compounds many of which have been shown to induce or promote carcinogenesis.¹² Some of these substances have been detected in e-cigarette solutions and mist but only scarcely have their levels been high enough to be considered dangerous.^{13,14} Williams et al found levels of lead, chromium, and nickel in e-cigarette aerosol to be equivalent to, and in some cases higher than, what has been reported for cigarette smoke.¹⁵

The physiological effects of vaping also display certain discrepancies in different studies. Most of them show that nicotine levels are considerably lower after e-cigarette use than smoking a conventional cigarette, although others report similar effects between vaping and smoking.¹⁶⁻²¹ With regard to clinical effects, the majority of researchers conclude that e-cigarette mist is less harmful. It has been shown less cytotoxic for embryonic stem cells and murine fibroblasts, and it produces smaller changes in functional pulmonary parameters. Moreover, Flouris et al demonstrated that acute smoking, but not acute vaping, induced increases in white blood cell count, lymphocyte count and granulocyte count; in a case report Farsalinos and Romagna reported that smoking cessation and e-cigarette use reversed symptoms of chronic idiopathic neutrophilia.²²⁻²⁵

In contrast to these results, Vardavas et al showed that five minutes of acute vaping induced a decrease in exhaled nitric oxide and an increase in airway resistance and impedance in experienced smokers, while quitting of vaping cured an exogenous lipid pneumonia in a case report by McCauly et al.^{26,27} Furthermore, a study in *in vitro* cultures of pulmonary fibroblasts and human embryonic stem cells displayed cytotoxic effects of chemical compounds contained in electronic cigarette devices.²⁸

Hence, the so far collected data with respect to the physiological and clinical effects of vaping are somewhat discrepant. Most reports advocate for a rather neutral impact on health and certainly suggest substantially less harm in comparison to smoking which is estimated at approximately 1% of the mortality risk of smoking.^{29,30} However, the publications indicating the negative effects of e-cigarettes cannot be ignored and the issue is still open until more trials evaluate the long-term consequences of their use.

A more prudent approach would be to invest on vaping as a tool in smoking cessation efforts, since this would probably require a short- to mid- term exposure to e-cigarette compounds, hopefully not exceeding 12 months. A 12-month study which randomized 300 smokers with no intention to quit smoking to two different e-cigarette dosing regimens and a placebo e-cigarette without nicotine, showed smoking reduction 22.3% and 10.3% at week-12 and week-52 respectively

and complete abstinence from tobacco smoking 10.7% and 8.7% at the same time intervals in all three groups without differences among them.³¹

The same team conducted a small trial in 14 schizophrenic patients and showed sustained 50% reduction in the number of cigarettes/day at week-52 in 7/14 (50%) participants (from a median of 30 to 15 cigarettes/day, $p = 0.018$) and sustained smoking abstinence at week-52 2/14 (14.3%) of the study population.³² Polosa et al followed 40 smokers started on electronic cigarette for 6 months and found 50% reduction in the number of cigarettes/day in 13/40 (32.5%) of them (from 25 to 6 cigarettes/day, $p < 0.001$), 80% reduction in 5/40 (12.5%) and complete smoking abstinence in 9/40 (22.5%).³³

In an online survey with a total of 222 respondents, at the end of a 6-month period, smoking abstinence was 31.0% (95% CI=24.8%, 37.2%). Smoking reduction reached 66.8% and temporary cessation was observed in nearly 50% of the sample. The number of e-cartridges used per day correlated with the outcome, a finding confirmed by others as well but not invariably present.³⁴ Interestingly, one third of the responders did not use any nicotine containing products at the time of evaluation.³⁵

A large trial with 657 participants compared the efficacy of e-cigarette with or without nicotine and nicotine patches by randomizing the study population in three groups in a 4:4:1 ratio (289 to nicotine e-cigarettes, 295 to patches, and 73 to placebo e-cigarettes) administered from one week prior to 12 weeks after smoking quit. At 6 months, biochemically verified abstinence was 7.3% with nicotine e-cigarettes, 5.8% with patches, and 4.1% with placebo e-cigarettes. The efficacy of all three methods was similar with the risk difference for nicotine e-cigarette vs patches being 1.51 (95% CI -2.49 to 5.51) and for nicotine e-cigarettes vs placebo e-cigarettes 3.16 (95% CI -2.29 to 8.61).³⁶ However, even in this trial the smoking cessation rate was lower than expected, leading to reduced statistical power and inability to elicit established conclusive results.

CONCLUSION

The electronic cigarette has gained significant popularity among smokers both as a substitute for conventional tobacco use and as an aid to smoking cessation. The delivery of harmful substances and elements via e-cigarette use seems substantially lower compared with conventional smoking but the effects of vaping in health status, especially after prolonged administration have not been fully elucidated yet. Therefore, a prolonged use of e-cigarettes as a substitute for conventional smoking is not advisable until more trials assess their long-term consequences. A more sensible ambition would be to employ vaping as a bridge to quitting, providing that after a reasonable time period e-cigarette will be discontinued as well. The initial trials have been encouraging towards this direction but more

research is needed to define the exact position of electronic cigarette in contemporary preventive medicine.

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