

Electronic cigarette

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Despite significant efforts during the last decades, cigarette smoking still remains prevalent. Discouraging the use of all tobacco products, it is certainly the most effective mean to enhance public health, but complete prohibition is unlikely to succeed. The greatest challenge is the approach to chronic smokers, particularly those affected with cardiovascular conditions. To better support these patients during the difficult process leading to complete smoke cessation, it is important to characterize each patient from a clinical and psychological perspective, introducing the most reliable approaches to incentivize and support abstinence, such as varenicline and nicotine replacement therapy, thus providing a personalized recommendation. The recent introduction of electronic systems for nicotine release or tobacco heating (electronic cigarettes), offers an important challenge. These devices are reasonably considered as *lower risk* tools, thus providing a useful alternative which enables the patient a smoother transition toward smoking cessation, also presenting an array of choices among which a personalized selection could be made. This technology, though, should not be overemphasized, considering also its potential harmful effects, and certainly its use should be strongly discouraged in non-smokers, particularly at young age. This approach, cautious and pragmatic, aside from demonization or over-enthusiastic appraisal, could provide favourable results in the constant struggle against cigarette smoking.

Introduction

Despite important advances in basic and clinical research, smoking continues to represent a formidable challenge for global health as for the individual.¹ In Italy alone, it is estimated that smoking causes at least 200 deaths every day, which would be totally avoidable if people refrained from smoking, and if smokers immediately ceased this dependence. Despite the best intentions, it is clear that totally prohibitionist approaches would be unsuccessful if not even counterproductive, as already demonstrated with alcoholic beverages in the USA almost a century ago. Hence the strategy adopted in most countries to discourage the use of cigarettes and other tobacco products through specific bans (e.g. smoking in public places), to make these products

more expensive with dedicated taxes, to modify the subjective perception of the smoker (through dissuasive packages, and prohibiting smoking in entertainment programs), and to inform potential smokers in detail and incisively.² Overall, these measures have proved to be quite effective and have overall reduced the prevalence of smokers, but only partially (*Table 1*). Important efforts are still needed to further reduce smoking. As a clinician, our challenge is not only to prevent smoking addiction but above all to inform and help our smoking patients to stop and remain abstinent. In particular, the smoker cardiac patient represents a great challenge, as many heart patients continue to smoke despite a significant clinical history of major cardiovascular events.

In fact, despite the usefulness of the 5A-based approaches (Ask, Advise, Assess, Assist, Arrange) and the 5R (Relevance, Risk, Rewards, Roadblocks, Repetition), few smokers independently succeed in quitting, and this is

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Table 1 Summary of clinical evidence on the prevention and cessation of cigarette smoking

(Strategies of proven, efficacy uncertain, strategy ineffective, or harmful strategies)

Bupropione drug therapy
 Cytisine
 Clonidine
 Nortriptyline
 Nicotinic replacement therapy^a
 Varenicline^a mecamylamine fluoxetine
 Hypericum
 Lobeline
 Moclobemide
 Naltrexone
 Paroxetine
 Selegiline
 Sertraline
 Nicotinic vaccines
 Venlafaxine
 Non-pharmacological therapy behavioural psychotherapy
 Electronic cigarettes
 Psychosocial therapy acupuncture
 Rehabilitation/physical therapy
 Other interventions media campaigns
 Legislative prohibitions
 Training of health personnel
 Economic incentives
 Paper-based educational materials
 Interactive programs via internet or smartphone
 Institutional regulations
 Institutional screening
 Use of electronic medical records Involvement of relatives and caregivers
 Motivational interviews
 Partner involvement

Based on a systematic screening of Cochrane reviews on the subject of smoking.

^aParticularly effective strategies.

true unfortunately also for smokers with a recent major cardiovascular event. Hence, the importance of a combined approach that in addition to integrated patient management also includes drug therapy (*Figure 1*). Among the various treatments tested to promote smoking cessation and abstinence, varenicline and nicotine replacement therapy are certainly among the most effective, especially if based on the combination of complementary instruments, such as chewing gum and patches. Bupropion also appears to have a favourable role in promoting cessation and abstinence, although of a lower level compared to varenicline and nicotine replacement therapy.³ Unfortunately, even systematically using such treatments, the probability for a chronic smoker to actually stop smoking is disappointingly low.

Recently, new electronic nicotine release systems (globally definable as electronic cigarettes, E-Cig) have been introduced among consumers, particularly attractive for smokers of combustion cigarettes.⁴ The E-Cig have evidently been developed and marketed for profit, and it is currently estimated that 5% of the adult population

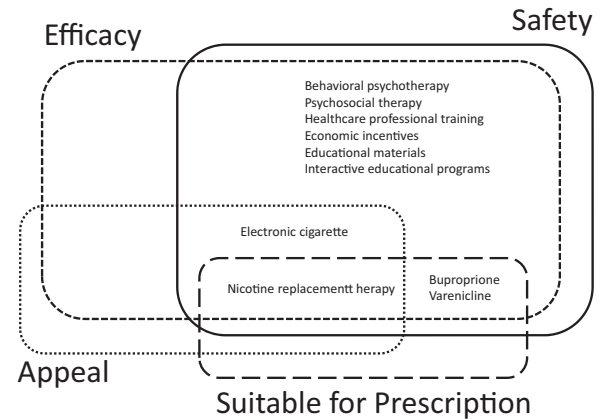


Figure 1 Strategies to promote cessation and abstinence from cigarette smoking in smokers, distinguishing four main dimensions: efficacy, safety, prescription, and palatability compared to the traditional combustion cigarette.

habitually uses E-Cig, with even greater estimates in some particular groups of subjects, such as adolescents.⁵ In a very pragmatic perspective, shortly after their introduction, their potential use was hypothesized to support traditional cigarette smokers in their cessation path.⁶ The purpose of this brief review is to summarize the main features of the E-Cig, highlighting their strengths and weaknesses and proposing a pragmatic approach for their conscious use by our patients.⁷ Preliminarily, it should be clarified however that with the present work we want to illustrate the possibility of prudently using the E-Cig as a strategy for reducing the risk among chronic smokers, but in no way stimulate or maintain a neutrality towards the use of E-Cig among non-smokers.⁶⁻⁸ This use should be strongly discouraged in order to avoid a new pandemic linked to the possible abuse of E-Cig in the next decades, for example among adolescents or together with products derived from cannabis.

What are E-Cigs?

Most of the E-Cigs are battery-operated electronic systems capable of generating an aerosol containing nicotine by heating a dedicated solution using a metal filament at a controlled temperature (50°C-250°C). Specifically, they are sometimes called electronic nicotine delivery systems. Among the most successful E-Cig, currently we can mention for example Blu (Blu, Charlotte, NC, USA) and Juul (PAX Labs, San Francisco, CA, USA).^{6,9}

In such devices, nicotine is dissolved in a liquid contained in a tank, along with various additives. This liquid is vaporized and then superheated by the aforementioned filament, thus more precisely generating an aerosol rich in micro-droplets with a consistency, taste, and smell relatively similar to that of the smoke generated by the combustion of tobacco. Therefore these E-Cig do not involve combustion, and commonly the term vaping or vapping is used rather than smoking, when referring to the E-Cig. The characteristics of E-Cig liquids are highly variable and incompletely known. Nicotine-free liquids are available,

others with varying concentrations and amounts of nicotine, and variously flavoured liquids. Liquids can also be customized, and even the addition of liquid cannabis products to E-Cig is not infrequent among adolescents.

Recently, some tobacco companies have proposed a variant of traditional E-Cig, based on controlled heating of tobacco leaves. These electronic devices are called heat-not-burn (HNB) or heat-not-smoke, and the most representative of these are glo (British American Tobacco, London, UK) and IQOS (Philip Morris International, Neuchatel, Switzerland).¹⁰ The peculiarity of these devices is the use of dedicated single-use cigarettes, whose tobacco is heated in a controlled way by a metal sheet up to 350°C. The E-Cig type HNB produces a smoke more similar to that of traditional cigarettes, also in terms of palatability, against a drastic reduction (but not complete elimination) of the combustion process. Furthermore, the same additives found in traditional E-Cig liquids are not present, although the typical contaminants of tobacco leaves are obviously traceable. It is therefore in many respects an intermediate product between traditional E-Cig and combustion cigarettes, both in terms of toxicity and appeal. In other words, it is likely that the E-Cig type HNB are less toxic than the combustion cigarettes but more toxic than the traditional E-Cig, compared to an appetite for the traditional cigarette smoker greater than that of the traditional E-Cig.

What are the risks associated with using E-Cig?

It is difficult to establish what the real risks of E-Cig are, since these were only marketed few years ago.^{9,10} Therefore, only the short-term risks of these devices can be assessed with certainty, while the risks in the long term they remain unknown (*Table 2*). Pragmatically, however, it is useful to distinguish the risks associated with nicotine intake (summarizing them briefly), the specific risks of traditional E-Cig, and the specific risks of E-Cig type HNB. The harmful effects of nicotine in the central, peripheral, gastrointestinal, and endocrine nervous system, among others, are known. Nicotine is also considered an indirect carcinogen, as it is capable of promoting carcinogenesis induced by other substances. The specific risks of traditional E-Cig depend substantially on the characteristics of the devices (e.g. the risk of overdosing on nicotine or battery explosion) and of the solutions (e.g. there are diluents with specific toxic effects such as polyethylene glycol). Instead, apart from the possible drawbacks linked to the device, the risks of the HNB type E-Cig are more similar to those of the combustion cigarettes, even if the emissions of toxic substances are clearly lower (with reductions of up to 95-99%).

Our group has studied in detail the vascular, oxidative, and platelet effects of traditional and HNB type E-Cig in the SUR-VAPES (Sapienza University of Rome-Vascular Assessment of Pro-atherosclerotic Effects of Smoking) studies.¹¹⁻¹⁴ In the SUR-VAPES study, the oxidizing and platelet effect of acute smoking of traditional combustion cigarettes and E-Cig was compared in 40 subjects (20 smokers and 20 non-smokers), showing that these had an oxidizing and pro-aggregating effect less intense than to traditional

Table 2 Potential risks and benefits linked to the use of electronic cigarettes compared to traditional combustion cigarette

Hepatotoxicity ^a
Creation of craft mixes (also containing cannabis products or other drugs)
Avoidance of smoking bans
Propylene glycol release ^a
Increased proatherosclerotic blood lipids
Risk of nicotine overdose
Risk of battery explosion acute and chronic global risk
Chronic cardiovascular risk
Chronic cancer risk
Chronic pulmonary risk
Risk linked to smoking during pregnancy and lactation
Risk associated with passive smoking
Risk related to use in adolescent age lower cost ^a
Less cytotoxicity
Less environmental contamination and passive smoke effects
Less endothelial dysfunction
Less pro-aggregating effect
Less pro-aggregating effect
Less carbonyl emission (formaldehyde, acetaldehyde, propionaldehyde, crotonaldehyde, and acrolein)
Less carbon monoxide emission
Less nicotine emission ^a
Less systemic inflammatory reaction and respiratory tract
Less oxidative stress

^aLimited to certain types of electronic cigarettes or specific methods of use (e.g. non-intensive aspiration).

cigarettes, especially in smokers.^{11,12} In fact, a specific sub-analysis of the SUR-VAPES study showed that the toxic effect of combustion cigarettes and E-Cig is typically less marked in chronic smokers, while it is clearly more pronounced in naive subjects.

In the SUR-VAPES 2 study, 20 smokers were randomized to smoke combustion cigarettes, traditional E-Cig, and E-Cig HNB type.¹⁴ All three types of cigarettes have shown an unfavourable acute impact on blood pressure, dependent endothelial vasodilation, oxidative stress, and platelet aggregation. HNB-type E-Cig showed a less severe hypertensive and oxidizing effect compared to other cigarettes, while showing an effect similar to that of traditional E-Cig in terms of dependent endothelial vasodilation and platelet aggregation. Moreover, the HNB type E-Cig appeared more attractive and satisfying than traditional E-Cig. Therefore, these results support the potential use of E-Cig as a reduced (but not zero) risk product to support smoking cessation and abstinence.

How can E-cigarettes be used consciously in chronic smokers?

E-cigarettes are not a medical device, there are no applications for approval from regulatory bodies as tools to promote abstinence from traditional cigarette smoking, and requests for indication as a low-risk product have also been denied.⁶ Therefore, we absolutely advise against considering E-Cig as a medical instrument. Smoking cessation should rather be based in the first instance on instruments

with proven efficacy and safety (Table 1, Figure 1). Nevertheless, how can we respond pragmatically to a chronic smoker who asks us our opinion about E-Cig?

The first approach, advocated for example by Stanton Glantz, a pioneer in the fight against smoking, is to advise against any type of use of E-Cig, in order to minimize the risks, motivating smokers to abstain and to adopt therapy with proven and favourable risk-benefit and cost-benefit ratio.⁶ Obviously we are not opposed to this strategy, but pragmatically and subjectively we are convinced that you risk throwing the child away with dirty water, and you risk losing an important opportunity.

In fact, the alternative approach, supported for example by Chris Bullen and others,^{6,15} is to inform smokers who are unable to stop smoking despite the use of dedicated therapies, on the possibility of using E-Cig with the aim of ceasing the use of combustion cigarettes (Figure 2). Expanding this approach, we consider it useful to use the E-Cig with the following objectives, in decreasing preferential order:

- (1) completely cease the use of the traditional cigarette and temporarily switch to the use of E-Cig, fixing in advance a future date for the cessation of the latter;
- (2) completely cease the use of the traditional cigarette and switch to the use of E-Cig, periodically re-evaluating the dependence on the latter in order to eventually fix the cessation;
- (3) temporarily reduce the use of traditional cigarettes (e.g. halving the number of cigarettes smoked daily) by adding the concomitant use of E-Cig, fixing in advance a future date for the cessation of traditional cigarettes and, subsequently, of E-Cig.

Similarly, in light of the likely differences in terms of safety and palatability between the different E-Cig, two alternative approaches can be distinguished:

- a. use of traditional E-Cig;
- b. use of E-Cig type HNB,

Obviously a type 1a approach is in many ways the most attractive, given the possibility of reducing by E-Cig the risks associated with traditional cigarettes (e.g. linked to carbon monoxide and carcinogenicity), however a pragmatic and individualized choice is essential to maximize the clinical effectiveness of E-Cig. For example, in a subject with a high dependency (Fagerström test score of 10), it is plausible that it is more effective to try first with the E-Cig type HNB than with the traditional ones, remaining ready to temporarily tolerate traditional cigarette and E-Cig, in order to allow the patient to familiarize himself favourably with the latter, and at the same time to part from combustion cigarettes.

Conclusion

The E-Cig, has plausibly a reduced risk compared to the combustion cigarette, and could become a useful tool to accompany the patient on his tobacco withdrawal path. However, this technology should not be underestimated in light of the specific potentially damaging effects on health,

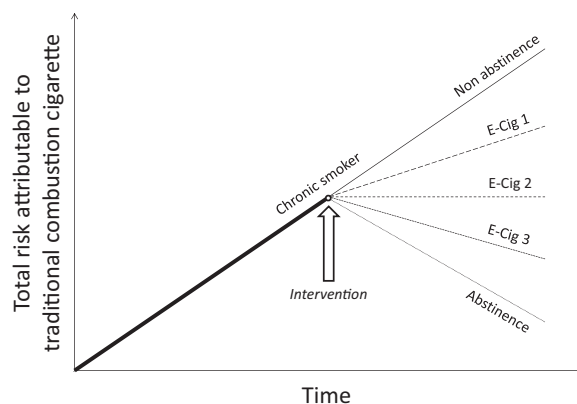


Figure 2 Summary diagram of the reduction of the clinical risk associated with cessation and abstinence from combustion cigarette smoke, and potential partial reduction of this risk by switching to the electronic cigarette (E-Cig). The arrow indicates the moment in which the subject smoker tries to stop smoking, considering various possibilities depending on his motivation to stop. Different scenarios are conceivable depending on the safety and tolerability of each E-Cig, but also on its capacity to motivate abstinence from the combustion cigarette. For example, an E-Cig at greater risk of toxicity and only partially motivating abstinence from the combustion cigarette (E-Cig 1) will be associated with a lower risk reduction compared to a particularly safe and strongly motivated E-Cig abstinence from the combustion cigarette (E-Cig 3). Products with intermediate characteristics (E-Cig 2) will give an intermediate risk reduction between these two extremes.

and its use should be explicitly not recommended for non-smokers. This cautious and pragmatic approach to the E-Cig, which avoids demonization, but also easy enthusiasms, will hopefully give the most favourable results in the fight against cigarette smoking.

Conflict of interest: none declared.

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