

Editorial

Cardiologists and Electronic Cigarettes



El cardiólogo ante el cigarrillo electrónico

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INTRODUCTION

The ongoing electronic cigarette debate has created a great deal of confusion. This editorial deals with certain questions in order to advise cardiologists about the growing phenomenon of electronic cigarettes: What are electronic cigarettes? Are they safe? Are they a public health concern? Can they help smokers quit smoking or reduce their risk? How are they regulated, and how should they be regulated? As cardiologists, what should we tell our patients? By answering some of these questions, perhaps we can shed some light on this confusing subject.

ELECTRONIC CIGARETTE CHARACTERISTICS

Electronic cigarettes are devices that use a coil and small battery to heat and vaporize a liquid solution, imitating the gesture of smoking a cigarette. Some of these vapors release nicotine, while others only have aromas and other substances like propylene glycol and glycerin. When the user “vapes”, the battery heats the atomizer and vaporizes the liquid solution, which is then inhaled. As there is no combustion, no carbon monoxide is produced. Traces of nitrosamines, formaldehyde, acetaldehyde, and heavy metals have been found in these devices, although in smaller quantities than in conventional cigarettes. The amount of microparticles detected is similar to that of conventional cigarettes.

The most important characteristic of electronic cigarettes is that they are an ever-evolving product. The market offers a wide variety of brands using different mechanisms that can modify the bioavailability of these inhaled products and their potential toxicity. Many artificial flavors that are prohibited in commercial cigarettes (coffee, fruit flavors, caramel, cola, etc.) are a sales gimmick for electronic cigarettes, whose marketing strategy is targeted at young people. Meanwhile, nicotine is present in most liquid cartridges at concentrations that vary from 0 to 36 mg/mL.

ELECTRONIC CIGARETTE SAFETY

Toxicity thresholds for the potentially toxic substances found in electronic cigarettes are unknown. Exposure to propylene glycol, for example, can cause respiratory and eye irritation. Although glycerin is considered safe for oral consumption, we cannot be sure of its safety when inhaled. Not many studies have been published about the biological effects of electronic cigarette exposure, although some indicate that it may cause increased resistance and oxidative stress of the airway.¹ As not enough evidence has been accumulated, the long-term effects are unknown. Thus, until their potential carcinogenic effect has been determined, these products should not be publicized as not causing cancer. Regardless, what cannot be denied is that nicotine is a powerful psychoactive substance that is highly addictive, as well as a potential cardiovascular toxin with sympathomimetic properties. It increases heart rate, myocardial effort, and oxygen demand, while also favoring platelet aggregation and coronary vasoconstriction. Given these effects, patients with established coronary disease are especially susceptible.² There have also been case reports of accidental nicotine intoxication due to these devices, mainly in children, for whom doses of more than 6 mg may be lethal. Furthermore, there is a certain controversy about the potential risks of passive vapor inhalation because electronic cigarettes release substances like propylene glycol and nicotine into the air, in addition to other microparticles. In any case, due to the lower concentrations of these substances, it can be assumed that the risk would be lower than that of second-hand smoke from conventional cigarettes.

ELECTRONIC CIGARETTES AS A SOCIAL PHENOMENON AND POTENTIAL PUBLIC HEALTH THREAT

Less than a decade has passed since Beijing pharmacist Hon Lik invented, patented, and later commercialized the first electronic cigarettes through his company, Ruyan, in 2004. Electronic cigarettes and their consumption have become spectacularly widespread, first in the United States and then in Europe, Japan, and other parts of the world. It is difficult to know how many users there are in the world. The total is surely more than 500 million worldwide, and

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leading manufacturers calculate the number as already exceeding 800 million. In the United States alone, it is estimated that the vaporizer market moves some 2 billion dollars per year.

Data from the Eurobarometer 2012 survey³ (26 000 citizens from 27 European countries) indicated that almost 30 million Europeans had tried electronic cigarettes. Most of them were between 15 and 24 years of age, smoked more than 20 cigarettes/day (“dual” users), and had tried to quit at least once in the previous year. When the data were analyzed by country, Spain was among the nations with the lowest rate of vaporizer use (10.9%), which was much lower than in countries like the Czech Republic (34.3%), Poland (31%), Luxemburg (28%), or France (22.6%). Spain was one of the countries with the highest proportion of people who considered that these electronic devices are a health hazard (48.9%), and this rate was higher than the European average (40.6%).

Since the end of 2012, we have witnessed an explosion of specialized stores (franchises) selling these devices here in Spain. Thanks to favorable economic conditions, including low start-up costs and a legal loophole that has allowed these products to be publicized and marketed with no limits whatsoever, selling electronic cigarettes is a business opportunity for some. The commercialization and advertising of these products are right on the cutting edge of today's marketing strategies (customization, “girly” products, celebrities, etc).⁴ The start of sales in tobacco shops in the autumn of 2013, along with the scientific and social debate around their usage, may have recently slowed this progression. Nonetheless, this does not mean that the phenomenon of electronic cigarettes and their multiple derivations is going to disappear, as we have witnessed how in other countries they are being sold through outlets other than specialized shops.

The aggressive marketing techniques and advertising of electronic cigarettes aimed at young people have been well documented. Evidence from the United States and South Korea show a rapid increase in the use of electronic cigarettes in young age groups, with worrying rates among young people who had never smoked a cigarette before.^{5,6} In addition, although the US FDA prohibits the sale of these products to minors (as in Europe), online sales of electronic cigarettes, with new brands and a multitude of different flavors and presentations, may circumvent regulation.

There is an intense, ongoing debate^{7,8} between those who believe that electronic cigarettes can be an aid to quit smoking that has fewer health risks vs those who fear that the consumption of liquid nicotine through electronic cigarettes can make smoking socially acceptable once again. This “renormalization” of smoking can be especially damaging among young people, who are the main foothold of the electronic cigarette market. This is the central threat to the prevention and control of smoking, especially in countries like Spain, where progress has been made only very recently⁹ and the balance is undoubtedly very fragile.

CAN ELECTRONIC CIGARETTES BE A TOOL TO QUIT SMOKING OR TO REDUCE THE RISK OF TOBACCO?

Many advertising campaigns for electronic cigarettes argue that they are effective for quitting smoking, but there is no solid evidence to support this claim. Some studies have found that electronic cigarettes with nicotine are effective in controlling abstinence symptoms,¹⁰ which does not necessarily mean that they are a good strategy for kicking the habit when used *ad libitum* and without a structured plan of use. Most studies show a tendency towards dual electronic cigarette/conventional cigarette use. In a meta-analysis of 4 longitudinal population studies and a crossover study, the use of electronic cigarettes by smokers was associated with a lower

rate of abstinence (odds ratio = 0.61; 95% confidence interval, 0.50–0.75).¹¹ The small number of clinical assays that have been published to date present certain methodological deficiencies (limited number of patients, lack of a control group, selection biases), and the results sometimes do not agree. Abstinence rates are generally low, and one randomized study found no significant differences between electronic cigarettes and nicotine patches.¹² There is solid evidence that supports the safety and effectiveness of pharmacological therapies to quit smoking, such as varenicline, nicotine substitutes, and bupropion. In conjunction with these therapies, motivational support increases the likelihood of abstinence. To be able to support electronic cigarettes as an effective, safe tool to quit smoking, it is necessary to accumulate comparable scientific evidence, which is currently lacking.

Some health care professionals support the use of electronic cigarettes as a strategy to lower patient risk, which in the realm of addictions refers to therapies aimed at reducing the risk and injury associated with the consumption of a substance. Although electronic cigarettes could be considered *a priori* less toxic than tobacco, the trend toward dual consumption in electronic cigarette users makes it difficult to achieve total cessation and instead favors bidirectional consumption of conventional and electronic cigarettes. Total cessation should be the priority in any tobacco control intervention program, especially within the context of cardiovascular risk prevention, due to the nonlinear dose-response relationship between smoking and cardiovascular disease. Nonetheless, it is true that nicotine is a highly addictive substance, and many smokers have enormous difficulties in their attempts at abstinence, even if they have developed smoking-related diseases or have undergone intensive therapies to quit smoking. To be able to consider electronic cigarettes a strategy for risk reduction, there needs to be a precise, evidence-based definition of the type of smoker for whom these interventions could be considered. Furthermore, the manufacturing and regulation of these products should meet standards for effectiveness, safety, quality, and efficiency.

ELECTRONIC CIGARETTE REGULATIONS

Although electronic cigarettes have been legally introduced as consumer products in several countries, none of these countries have approved them as medication; therefore, the claim cannot be made that these electronic systems are effective products to quit smoking or to reduce damage. Manufacturers of these devices have benefitted from the current gap in regulation, evading the fact that nicotine is a potentially dangerous substance if its use and manipulation do not meet certain stipulations.

There have been some reports of success in many countries that have adopted clear legislative measures. Australia prohibits the importation and sale of cartridges that contain nicotine. Brazil and Turkey have prohibited importation, sale, and publicity of electronic cigarettes until manufacturers provide information about their safety. There are multiple international approaches and a veritable kaleidoscope of regulations, which will tend to merge in coming years.

The World Health Organization has been a leader in the international debate in this matter and has called for caution and discretion.¹³ A regulatory framework requires that manufacturers present data about safety and efficacy. In this case, the use of these devices as an aid in smoking cessation (if scientific evidence were to support it) would be carried out under the supervision of a regulatory health authority that would verify manufacturers' claims, regulate product engineering, establish warnings for possible risks, and require ingredient lists and safety data.

In Europe, after months of intense parliamentary debate, the Tobacco Products Directive 2014/40/EU of the European

Parliament¹⁴ established, among other measures, that electronic cigarette manufacturers should produce either medicinal or tobacco products. It also regulates the maximum quantity of nicotine (20 mg/mL or 2 mL per refill) and bans cross-border advertising.

In Spain, a few months after regional initiatives and those of relevant scientific organizations had become known,¹⁵ the Health Care Ministry promoted new legislation that begins to close the regulatory gap. Law 3/2014 (27 March 2014)¹⁶ provides additional clauses for Tobacco Law 28/2005, prohibiting the use of electronic cigarettes in public administration buildings, bathrooms, health-care centers and hospitals, educational institutions, parks or outdoor play areas for children, and on any type of public transportation, as well as sea transportation, trains, or airplanes. Advertising of these products is prohibited during television programs targeted at minors under the age of 18 and for the 15 minutes before and 15 minutes after said programming. There will be no advertising for these products from 4 pm to 8 pm, and no minors under the age of 18 can appear in these ads. Last of all, no claims can be made about their effectiveness or any sort of therapeutic indications unless they are specifically corroborated by a competent health care organism.

THE USE OF ELECTRONIC CIGARETTES IN PATIENTS WITH HEART DISEASE

Patients are going to ask us lots of questions about safety, utility, and the potential value of changing to electronic cigarettes. When answering them, it is important to have some clear ideas. A recent publication¹⁰ emphasizes that we should support attempts at quitting smoking and make sure that our advice does not put a damper on patients' motivation. Moreover, we should support their decision to try to quit smoking and recommend a treatment plan including, among other things, a quit date to stop smoking, along with advice and recommendations about the most effective and safest cessation treatments: varenicline, nicotine substitution therapy, and bupropion.

Having said this, supporting the decision to quit smoking of a patient who wants to use electronic cigarettes does not mean that we have to approve the use of these devices. If the patient has failed with an initial treatment, does not want to use a conventional treatment, and wants to use electronic cigarettes no matter what, it would be reasonable to support the attempt at quitting. Meanwhile, however, we should inform patients that there is not sufficient evidence about electronic cigarettes' safety or their effectiveness in smoking cessation, and explain that the compositions of these products can vary greatly from brand to brand. Given the positions of the World Health Organization, the Spanish Society of Cardiology, and the Spanish National Committee for Smoking Prevention, we believe that our stance as cardiologists should be prudent and we should advise our patients against their use. The best we can do is to offer them alternatives with demonstrated efficacy, safety, and quality, including medication and cognitive-behavioral therapy.

CONCLUSIONS

Today, electronic cigarettes can be considered consumer products that are similar to conventional cigarettes. They are insufficiently regulated and contain potentially toxic and pharmacologically active substances in unknown quantities, with no demonstrated effectiveness as treatment for smoking cessation or reduction of the harms of tobacco.

As for the safety of these devices, we do not know whether they are safe. Nor do we know if they would continue to be so in the

short- to mid-term when subjected to the arbitrary modifications of manufacturers who could (and why not?) make them more addictive and more dangerous, just as happened in the past with conventional cigarettes.

Electronic cigarettes are a public health threat and cannot be considered an aid to quit smoking or to reduce tobacco risk as long as there is no solid evidence to corroborate this claim or regulations to guarantee their quality, effectiveness, and safety.

In the end, perhaps the debate is artificial and the question at hand is simpler than it seems. There are two possible scenarios. In the first, electronic cigarettes would be devices designed for a therapeutic end: to help smokers quit smoking or to reduce the damage caused by tobacco. In this case, these products would have to be regulated by drug administrations (European Medicines Agency, U.S. Food and Drug Administration, and similar organisms) under current quality regulations and after having proven their safety, effectiveness, and quality in clinical trials in order to be commercialized as therapeutic devices.

In the second scenario, electronic cigarettes would be consumer products that could administer highly toxic and addictive substances, such as nicotine, in addition to other scarcely regulated additives. In that case, the commercialization of electronic cigarettes should follow regulations that are at least equally restrictive as current tobacco regulations and be met with firm opposition from medical professionals and scientific societies.

CONFLICTS OF INTEREST

J. Fernández de Bobadilla directed a project that studied the correlation between legislation prohibiting smoking in public places and cardiovascular disease, financed by an unconditional grant from Pfizer.

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