Arch Bronconeumol. 2019;55(11):581–586

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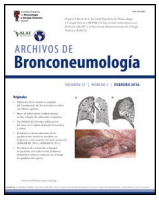

SEPAR's voice

Official statement of the Spanish society of pulmonology and thoracic surgery (SEPAR) on electronic cigarettes and IQOS®☆

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ARTICLE INFO

Article history:
Received 4 February 2019
Accepted 29 April 2019
Available online 19 September 2019

Keywords:
Electronic cigarette
IQOS®
Tobacco
Risks
Safety
Effectiveness

ABSTRACT

The use of novel tobacco products, particularly the electronic cigarette (EC) and partial tobacco combustion devices (HnB systems: Heat not Burn), has increased exponentially, particularly among adolescents and young people. The health authorities and scientific societies have shown concern about issues surrounding safety and effectiveness (as a method of smoking cessation). A study of the available scientific evidence has concluded that the safety of the vapor or fumes inhaled by the users of these devices cannot be guaranteed. Contradictory results from various clinical trials and meta-analyses also mean that these devices cannot be recommended for their effectiveness in cessation, especially when safe and effective treatments are available to help quit smoking (varenicline, nicotine replacement therapy, and bupropion, combined with psychological counseling).

Declaración Oficial de la Sociedad Española de Neumología y Cirugía Torácica (SEPAR) sobre cigarrillos electrónicos e IQOS

Palabras clave:
Cigarrillo electrónico
IQOS®
Tabaco
Riesgos
Seguridad
Eficacia

RESUMEN

El uso de productos del tabaco novedosos, en especial el cigarrillo electrónico (CE) y los dispositivos de combustión parcial de tabaco (sistemas HnB: Heat not Burn), ha aumentado de forma exponencial, sobre todo en jóvenes y adolescentes. Las autoridades sanitarias y las sociedades científicas han mostrado preocupación ante las dudas que existen sobre su seguridad y eficacia (como método de abandono del tabaco). Tras el estudio de la evidencia científica disponible, no es posible asegurar la inocuidad de los vapores o humos que inhalan los usuarios de estos dispositivos. Respecto a la eficacia, no pueden recomendarse, tras los resultados contradictorios, de diferentes ensayos clínicos y metanálisis; máxime cuando existen tratamientos seguros y eficaces para ayudar a dejar de fumar (vareniclina, terapia sustitutiva con nicotina y bupropion, unido a asesoramiento psicológico).

Introduction

Tobacco control strategies, implemented in developed countries for several decades now, have led to the emergence of new actors, electronic cigarettes (EC), and novel tobacco products[1] in the shape of Heat not Burn (HnB) systems, touted as risk-modifying devices.[2]

☆ Please cite this article as: Signes-Costa J, et al. Declaración Oficial de la Sociedad Española de Neumología y Cirugía Torácica (SEPAR) sobre cigarrillos electrónicos e IQOS®. Arch Bronconeumol. 2019;55:581–586.

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1579-2129/

The health authorities have repeatedly pointed out the negative impact that attaching "safety" or "low risk" messages on tobacco products have on control strategies.[3]

ECs are included among the so-called "electronic nicotine delivery systems". They consist of a cartridge which contains a liquid, with or without nicotine, a battery that when activated heats the liquid, and an atomizer that transforms the heated liquid into an aerosol.

HnB devices heat the tobacco to high temperatures (>350°C), without reaching the 900–1200°C levels that are obtained with conventional cigarettes (CC).[4]

A few years ago, our scientific society, SEPAR, clearly set out its position with regard to ECs.[5] Similarly, the Forum of International Respiratory Societies, an association of the main international scientific societies in the field of lung health, published a statement on these devices.[6] The aim of both documents was to disseminate updated written scientific knowledge and to express concern about the safety of ECs and the risks that "normalizing" their use could, and indeed does, have.

The initial concern has been seen to be well founded. We have witnessed an exponential increase in sales of these devices, with some tobacco companies entering the market, and the initial deterrent messages have even given way to scientific societies recommending these products[7] as a strategy for quitting nicotine dependence. Nevertheless, uncertainty persists, and recently the European Respiratory Society has clearly positioned itself against the use of ECs.[8] For this reason, the SEPAR believes it is time to release a new document, with up-to-date evidence on safety and effectiveness. The following methodology was followed in the preparation of this document:

1) The principal author conducted a literature search for articles related to the safety and efficacy in smoking cessation of ECs and the safety of I-Quit-Ordinary-Smoking (IQOS®) devices.

The search was conducted in 2 multidisciplinary databases that provide citation data, Science Citation Index Expanded of the Web of Science group, owned by Clarivate Analytics, and the Elsevier Scopus database (which includes the entire Medline/Pubmed database).

The search query was entered in the Topic field (which includes title, abstract and keywords). Document types were limited to article and review, no date limits were set, and documents that had been included up to the year 2018 were retrieved (date of the search 1 December 2018). The article published by Hajek et al. was subsequently detected (NEJM), and given its importance, was also included for analysis.

The terms (descriptors) used in the search were: smoking; tobacco; electronic cigarette*; electronic nicotine delivery system*; smoking device*; Heat not Burn tobacco product*; non-cigarette tobacco product*; e-cigarette*. Quotation marks were used so that the terms would appear in the search equation as described verbatim in the sequence, and some of the terms were truncated (with an asterisk), in order to retrieve all possible variants of the same term (for example: cigarette*, retrieves both cigarette and cigarettes).

The strategy was the following:

TITLE-ABS-KEY (smoking OR tobacco OR "electronic cigarette*" OR "electronic nicotine delivery system*" OR "smoking device*" OR "Heat not burn tobacco product*" OR "non-cigarette tobacco product*" or "e-cigarette*") AND LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "re").

1) Articles obtained from both databases were reviewed independently by the 2 principal authors, who subsequently came to an agreement, excluding those that were not pertinent, appropriate or relevant, thus extracting the documents with the greatest evidence.

Positioning will be based on the following schema:

1 Epidemiology.
2 Effects on health/safety.
3 Effectiveness as a method of smoking cessation.
4 Conclusions.

Epidemiology

Electronic cigarettes

The use of ECs has expanded throughout the world, doubling between 2008 and 2012. There are currently more than 460 brands, including models such as pod mods, for example the high-selling JUUL® system, that can release high doses of nicotine.

In a survey conducted in the United States, between 9%–13% of respondents over the age of 18 had tried ECs and between 2%–6% reported use in the last 30 days, and this form of nicotine consumption was more common among young adults.[9]

The National Youth Tobacco Survey[10] found that more than 3.5 million American students regularly use ECs, a habit that has been listed as an epidemic by the FDA, which is calling for greater controls on sales, especially to children.

Data from the 2017 Eurobarometer[11] report that 9% of respondents occasionally use ECs and 2% are regular users. Between 2014 and 2016, the number of individuals who had tried them at least once rose from 12% to 15%. There are large differences in consumption between countries (in the United Kingdom, 5% are regular users). With respect to the pattern of use, more than 50% report that they do not find these devices useful for cutting down smoking (52%), 17% have managed to cut down, and only 14% has stopped smoking with ECs.

Data from the latest survey on drug use in secondary schools in Spain[12] (ESTUDES 2016) indicate that 20.1% of students have used ECs on some occasion. Use in men ranges from 15% at 14 years of age and 32% at 18 years, and between 11% and 21% in women. Use is greater in smokers, in whom rates are higher than 40%, while 21% of EC users had never smoked tobacco previously.

The use of ECs can lead to the use of CCs among young people who in other circumstances would not have smoked. A study[13] in adolescents aged 14 years who had never tried combustible tobacco, followed for 6 and 12 months, showed that the use of ECs increases the possibility of initiating tobacco use (adjusted OR: 2.73; 2.00–3.73).

Heat not burn devices: IQOS®

Few epidemiological studies have been published on the use of IQOS®. A Japanese study on the knowledge of ECs and HnB products conducted in 2015 found that 48% of respondents were aware of these products and 6.6% had used them at some time. In total, 8.4% of the respondents had tried IQOS®.[14]

With regard to use in Europe, a survey carried out in Italy after the launch of IQOS® is of particular interest. Twenty percent of respondents were aware of the system and 1.4% had tried it. About half of IQOS® users (45%) and people interested in trying it had never been smokers. If we extrapolate these data to the general population, more than 730,000 Italians had tried it, 329,000 of whom were not smokers of CCs.[15]

According to data from Philip Morris International (PMI),[16] IQOS® is already used by more than 5 million people worldwide. In Spain, cumulative sales of 100,000 units are estimated. The fact

that IQOS® is considered a low-risk tobacco product means that the fiscal regime of CCs does not apply, and health warnings appear on only 30% of the packaging. For all these reasons, and in view of the experience in Italy,[15] an increase in consumption over the next few years is likely as users progressively attempt to replace CCs.

Effects on health/safety

Electronic cigarette

The design of the EC, the composition of the liquid, and the pattern of use all play a part in affecting health.[17]

In addition to nicotine, carcinogenic substances and ultrafine particles have been identified in EC aerosols. The most significant carcinogens include tobacco-specific nitrosamines, aldehydes, volatile organic compounds, and polycyclic aromatic hydrocarbons. The ultrafine particulate matter is significant for its heavy metal particles. These particles, with a diameter of less than 0.5 microns, penetrate the lungs easily and reach the bloodstream, and are then distributed throughout the body, causing damage to multiple organs and systems. There is evidence that, with the exception of nicotine and some metals, in typical conditions of use, exposure is lower than with tobacco smoke, but by no means less toxic.[17–20]

Biological effects of electronic cigarette aerosols

Recent studies have shown that EC aerosols may induce acute endothelial cell dysfunction and can also promote the formation of reactive oxygen species (oxidative stress).[21,22]

Nicotine is present in varying amounts. In experienced users who consume greater amounts of ECs, nicotine consumption can be similar to that of CCs.[18]

Surfactants such as propylene glycol and glycerol are safe in liquid form, although it is not known with certainty if they have the same properties when used in the form of aerosols. The same is true of the more than 150 EC flavoring chemicals,[23–26] which contain toxic carbonyl compounds (formaldehyde, acetaldehyde, acrolein and glyoxal) derived from the thermal decomposition of propylene glycol, glycerol, and flavorings. Formaldehyde is classified as a human carcinogen (Group 1), and acetaldehyde is a probable carcinogen (Group 2B).[27]

Radicals and reactive oxygen species are detected that cause oxidative stress and damage cellular proliferation and metabolism. Volatile organic compounds and phenols also occur, along with other substances such as furans, phthalate diethyl malonate and diethylhexyl phthalate. Various metals have been detected, such as chromium, nickel, lead, manganese, aluminum, tin, and iron, sometimes in quantities exceeding that of CCs[19,21,22]

In vivo studies in humans found data on oxidative stress and endothelial dysfunction, with increased cardiovascular risk markers and increased levels of circulating endothelial progenitor cells (EPC) after exposure to ECs of the same magnitude as that produced by tobacco smoke.[21,22,28] Other authors[29] found both *in vivo* and *in vitro* evidence that exposure to ECs causes levels of oxidative stress similar to tobacco smoke. Most studies conclude that ECs induce less oxidative stress than tobacco smoke.[30]

Effects of electronic cigarette aerosols on the cardiovascular system

At present, the results of the different studies indicate that the use of ECs is associated with cardiovascular disease and subclinical atherosclerosis, but we lack confirmatory evidence from long-term epidemiological studies. With regard to the acute effects, EC devices that use higher powered batteries show a steady increase in heart rate after use.[31]

Another study found that switching from CCs to ECs slightly decreased systemic blood pressure at 52 weeks in a group of smokers.[32]

Carcinogenic effects of electronic cigarette aerosols

Hypothetically, the risk of cancer with ECs would be less than that associated with CCs, due to the reduced number and amount of potentially carcinogenic substances. However, there is uncertainty surrounding the carcinogenic capacity of other highly DNA reactive substances, such as formaldehyde and acrolein, which can cause tumors in laboratory animals.

No long-term epidemiological studies have measured outcomes, such as the presence of tumors or intermediate cancer endpoints after exposure to ECs, although some studies show that rats exposed to EC aerosols develop DNA changes and mutations in urine.[33]

Effects of electronic cigarette aerosols on the respiratory system

Pulmonary exposure to ECs could damage the respiratory system or worsen pre-existing lung disease. Studies have been published that examine smokers with previous lung disease who switch from CCs to ECs (single or double use). No changes were found in lung function, although both quality of life and the number of exacerbations improved.[34] A notable limitation of these studies is the sample size.

Some of the studies that examine the effects of ECs suggest that devices that contain nicotine can have short-term adverse effects on pulmonary defense mechanisms.[35]

Cross-sectional studies that examine the impact of ECs on the respiratory health of adolescents found a significant association between the use of ECs and the presence of respiratory problems, asthma exacerbations, and school absenteeism.[36]

Effects of electronic cigarette aerosols on infectious defense mechanisms

With regard to the risk of infections, EC vapors increase pneumococcal adherence to the epithelial cells of the airway, both *in vitro* and in an experimental model with rats. These findings suggest that ECs can increase susceptibility to pneumococcal infection.[37]

Regarding oral disease, a review of the risk of cancer concludes that recommendations on the use of ECs should be viewed with caution, given the possible cumulative effect of mutations.[38]

A study found that similar levels of tobacco-specific nitrosamines are found the urine of non-smokers exposed to ECs and individuals exposed to CC.[39]

Heat not burn devices: IQOS®

These devices were first marketed in Japan in 2013 (Ploom®, Japan Tobacco Company, JTC). The IQOS® *(I Quit Ordinary Smoking)* model was developed by PMI. It has been marketed in Spain since 2016 and is available in 43 countries. It is presented as a less harmful product than CCs, and in the United States, PMI applied to the FDA for labeling as a low-risk tobacco product, but this was refused.[40]

These devices use battery-powered heating systems to increase the temperature of the tobacco without achieving total combustion. The temperature reached with IQOS® produces smoke that contains fewer toxic substances than CCs.[4] However, it has been shown that volatile compounds, polycyclic aromatic hydrocarbons, and carbon monoxide (CO), and even elements derived from pyrolysis are released in the mainstream emissions of the device.[41]

Most publications that minimize the risk to health of using IQOS® are studies sponsored by tobacco companies, and their safety conclusions have been questioned. A recent review[42] collected data available to date on emissions from these products; of the 31 studies retrieved, 20 were associated with tobacco companies.

Data have been obtained on the levels of harmful and potentially harmful constituents (HPHC) in the mainstream emissions of IQOS®, although only 2 of the studies were published by independent authors.[41,43] When the data are compared with the results of the studies sponsored by the tobacco industry, no differences were found in levels of CO, water, and the total number of particles; however, lower levels of tar (nicotine-free dry particulate matter) and higher levels of tobacco-specific nitrosamines delivered by the IQOS® device were detected.[44,45]

The results regarding particles in secondhand smoke from IQOS® are contradictory. HPHC is detected in air at lower levels than from CCs, but the content of the emissions varies considerably between the different studies.[42] In an independent study,[43] acrolein, an irritative substance, was detected, but not in the studies sponsored by PMI.

Glantz[46] has reviewed PMI data on the levels of potentially harmful biomarkers in IQOS® compared to CCs. No significant differences were found in 23 of 24 studies analyzed, leading the author to conclude that the statistical analyses were manipulated.

Nabavizadeh[47] analyzed the effect of IQOS® on the vascular endothelium using arterial flow-mediated dilatation, a validated measure of cardiovascular effect. The effects in rats which inhaled IQOS® are comparable to the effects of CCs.

To end this safety section, we wish to point out the interest that some studies show in demonstrating that the toxicity of ECs and HnB devices is less than that of CCs, when what we really need to take into account is that the respiratory apparatus must not be gratuitously exposed to any harmful substance (even if, as they insist, CC smoke is worse).

Effectiveness as a method of smoking cessation

Electronic cigarettes

Since their launch, ECs have been continuously promoted as a tool for smoking cessation. The clinical trials published to date have not been able to fully clarify this issue.

Bullen[48] reports the results of 657 smokers willing to quit, randomized to nicotine patches, ECs, or placebo. ECs were recognized as moderately effective, and significant methodological deficiencies were observed,[49] the most important being the lack of a double-blind design, differences in therapeutic adherence (around 80% in the EC group and 46% in the group that received patches), and the fact that ECs were shipped directly free of charge to homes, while patches had to be purchased in pharmacies.

Another non-blinded clinical trial[50] was conducted in smokers who had no intention to quit smoking. Finally, a study[51] also conducted in smokers with no intention to quit used an unconventional methodology and a short follow-up of scarcely 5 months.

Therefore, the first Cochrane meta-analysis[52] performed in 2014 concluded that confidence in ECs assisting in smoking cessation was low. A new revision was published in 2016,[53] in which the usefulness of the EC in helping smokers to quit was re-examined on the basis of 15 articles that met the selection criteria. Two randomized controlled trials with a total of 662 participants were analyzed, revealing that ECs containing nicotine may help smokers to quit for a period of 6–12 months compared with placebo. However, the authors added that due to the small number of trials, the imprecise nature of the studies, and the wide confidence intervals, confidence in the results was low, so the quality of evidence, according to GRADE standards, was classified as low or very low.

Another study[54] evaluated the association between ECs and smoking cessation in adult smokers, regardless of their motivation, and found that the likelihood of quitting smoking was 28% lower in the group that used ECs (OR 0.72, 95% CI: 0.57–0.91)

Another study,[55] aimed at generating new real-life evidence on the effectiveness of ECs in helping young adults to quit smoking, found that the odds ratio adjusted for smoking cessation was lower when using ECs compared with individuals who did not use them; the authors concluded that no evidence was available to claim that ECs were useful to help quit smoking. Similarly, Rigotti et al.,[56] in a study that sought to determine whether the use of ECs after discharge from hospital was associated with cessation in smokers who were planning to quit, found that individuals who used ECs after discharge were less likely to remain abstinent 6 months later than those who did not use them.

A recent clinical trial[57] compared the effectiveness of ECs with nicotine-replacement therapy (NRT). The cessation rate at 1 year was 18% with ECs compared to 9.9% with NRT (adjusted RR 1.75 [1.24–2.46]). This study has important methodological limitations: for example, it is not double-blind or placebo-controlled; at the 4-week follow-up, only 10.3% of the individuals who received patches were using them, while 53% of those who received ECs continued. Another potentially alarming aspect is the fact that 80% of EC users continued using them 12 months later, compared to 9% of the NRT group. This suggests that EC can create addiction, and smokers would appear to be switching from 1 addiction to another, with the public health problems that this might imply.[58]

For this reason, we currently do not have sufficient scientific evidence to conclude that ECs help to reduce the consumption of cigarettes or quit smoking. We need more independent research, randomized, double-blind, placebo-controlled clinical trials with no methodological deficiencies, and more rigorous observational studies conducted in real life to answer our questions and determine whether EC might be useful in helping to reduce tobacco use and quit smoking.

Heat not burn devices: IQOS®

There is no evidence to suggest that HnB devices could be useful for smoking cessation. Furthermore, the experience[59] observed in some countries shows that users of IQOS® become smokers of both ECs and CCs.

Conclusions

Our analysis, conducted using the available evidence, prompts the SEPAR to conclude with a few warnings about ECs and HnB devices, in particular IQOS®, the only system available in Spain.

The growth experienced by ECs, in particular the so-called pods, has alarmed the health authorities, since teenage users of Juul® (a type of pod that contains high amounts of nicotine) have levels of urinary cotinine that are almost double those found in smokers of CCs.[60] This confirms initial fears that these devices are becoming a gateway to nicotine addiction.

Even though tobacco companies insist that their devices replace CCs, the reality is that smokers become dual users.

Studies carried out in ECs and IQOS® confirm that the emission of toxic substances is quite probably lower than with CCs; however, it is clear that safety in the short, medium and long term is not guaranteed. Moreover, there is a demonstrated risk to people, especially children, who passively inhale the fumes and vapors of these devices. It should be noted that toxicity should not be compared between CCs and these devices, but between the use of these

devices and abstinence from any type of tobacco use. It is not natural to smoke.

With regard to effectiveness in smoking cessation, we currently we do not have sufficient scientific evidence (randomized, double-blind, placebo-controlled clinical trials with no methodological deficiencies and more rigorous observational studies) to conclude that ECs help to reduce the consumption of cigarettes and quit smoking. This, coupled with the safety problems associated their use, means that these devices cannot yet be recommended as a treatment for smoking cessation, especially when we currently have sufficient scientific evidence that demonstrates that the only safe and effective treatment for help quitting smoking is the use of drugs (varenicline, NRT, and bupropion)[61–63] in combination with psychological counselling.

Conflict of interests

JS-C has received honoraria for presentations, participation in clinical studies, and publications from: AstraZeneca, Boehringer, Ferrer, GSK, Menarini, Pfizer, and Rovi.

JIG-O has received honaria for presentations, participation in clinical studies, and publications from: AstraZeneca, Esteve, Gebro, Menarini, Pfizer, and Rovi.

ARP has received honoraria for presentations, participation in clinical studies, and publications from: AstraZeneca, Esteve, Ferrer, MundiPharma, Novartis, and Pfizer.

ACE states no conflict of interests.

EHM has received honoraria for presentations, participation in clinical studies, and publications from: AstraZeneca, Chiesi, Esteve, Ferrer, GSK, MundiPharma, Novartis, and Pfizer.

CRC has received honoraria for presentations, participation in clinical studies, and publications from: Esteve, GSK, MundiPharma, Novartis, and Pfizer.

ECC states no conflict of interests.

CAJ-R has participated in studies and given presentations for pharmaceutical companies that produce and market drugs for smoking cessation

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