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Emerging and alternative solutions to smoking addiction in the patient with a respiratory pathology

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Abstract

Smoking is the leading cause of morbidity and mortality worldwide and exposure to tobacco smoke is a risk factor in developing a respiratory pathology. Given the lack of success of pharmacological treatment and behavioural therapy in patients who cannot or do not want to quit smoking, emerging strategies are an alternative to conventional cigarette use. These strategies, such as electronic cigarettes and heated tobacco products, could be presented as an option to reduce, at least partially, the damage caused by tobacco, thanks to the absence of combustion of organic matter. This review shows how the use of these devices presents both an objective and a subjective improvement in COPD patients, reducing the development and progression of the disease, and reducing the biomarkers of exposure to toxic substances compared to continuing with the smoking habit.

Keywords: Tobacco use; COPD; Heat-not-burn tobacco; E-cigarette

1. Introduction

Smoking is the leading cause of morbidity and mortality in our country and worldwide. An estimated total of 52,000 deaths are attributed to this addiction per year [1]. According to the survey EDADES [2], carried out in Spain by the Ministry of Health and Consumer Affairs (before the COVID-19 pandemic), the prevalence of tobacco use in 2019-2020 was 44.4% for men and 34.2% for women, both aged between 15 and 64 years.

According to the European Survey of Health in Spain (EESE) 2020 [3], tobacco use in daily smokers is 19.8%, while in occasional smokers it is 2.3%. The average age that daily smokers start to smoke is at 17.7 years, and the average number of years of smoking daily is 21.8 years. However, data from the 2017 National Health Survey [4], carried out by the Ministry of Health and the Spanish National Statistics Institute (INE), indicated percentages of daily smokers at 22.1% and occasional smokers at 2.3%. This data included the average age for starting smoking in daily smokers as 17.4 years, very similar to the result of the EESE.

The percentages of tobacco use tend to decrease over time. But despite this, smoking remains a major problem for public health. Additionally, smoking has a significant impact on individuals, primarily on the respiratory and cardiovascular systems [5]. For this reason, all decisive and effective interventions are essential.

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2. Tobacco and respiratory pathology

There are five main respiratory pathologies that generate the greatest burden on the health systems, and two of them are caused by tobacco, i.e. chronic obstructive pulmonary disease (COPD) and lung cancer. In addition, smoking has direct implications in respiratory infections and asthma exacerbations. Tobacco smoke exposure, along with air pollution and workplace exposure to unsafe air, are the most important causes of respiratory pathologies [6]. The most prevalent respiratory disease is COPD. It has been proved that there is a relationship between COPD and smoking as an aetiological factor [7] (Table 1 [8]).

Table 1 Affectation and/or deaths due to respiratory pathologies

Disease	Affectation and/or deaths caused per year worldwide [8]
COPD	It affects more than 200 million, being moderate or severe in 65 million
Asthma	It affects 334 million and causes 489,000 deaths
Acute respiratory infections	They cause more than 4 million deaths
Tuberculosis	It affects 10.4 million and causes 1.4 million deaths
Lung cancer	It affects 14.1 million and causes 1.6 million deaths

The aetiology of the respiratory pathology is diverse. However, in diseases such as COPD, one of the most clearly implicated and well-defined factors is the use of tobacco. 90% of COPD patients are smokers. The habit begins at an early age, most often in adolescence (90% of smokers). The consequences of starting at such an early age give rise to respiratory diseases (COPD, lung cancer, and acute respiratory infections, Table 1) as well as the exacerbation of other diseases, such as asthma and tuberculosis. In addition, there is a higher number of lower respiratory tract infections in adolescent passive smokers [9].

Passive smoking plays an important role in the appearance or exacerbation of respiratory pathologies. Exposure to the toxins present in tobacco smoke through involuntary inhalation is associated with the appearance of cotinine in the urine of passive smokers. The measures taken by governments against secondhand smoke (such as the ban on smoking in public places) bring important health benefits in terms of respiratory diseases. Additionally, they also encourage smoking cessation, and reduce the relapse rate of smokers in the process of cessation [10].

Tobacco smoke contains a complex mixture of approximately 4,700 chemical compounds, including an alarming high concentration of oxidants. When smoke is inhaled not only are lesions generated in the lung parenchyma, but inflammatory mechanisms are activated as well. Although there are few studies conducted in human beings, it has been shown that oxidants act against the smooth muscle of the respiratory tract, causing the contraction of its fibers or enhancing bronchial hyperresponsiveness. These processes reduce the production of endothelin 1 and generate an increase in vascular permeability. Also, the increase in oxidising agents gives rise to an imbalance that can cause an inflammatory response. In fact, inflammation is the determining factor in COPD [11].

An increase in both tissue necrosis factor (NFκβ) and apoprotein 1 is observed in COPD patients. And both are responsible for the production of cytokines involved in airway inflammation and of powerful oxidising agents, such as interleukins 6 and 8 and TNF-α [12]. This, together with the redirection of neutrophils towards the pulmonary microcirculation that occurs in smokers with COPD, highlights the relationship between oxidative stress and the inflammatory reaction typical of this entity [13].

COPD patients have been found to have very high values of exhaled carbon monoxide (CO), which is possibly masked by tobacco use. In fact, it has been proven that exposure to tobacco smoke induces an increase in the heme oxygenase activity in fibroblasts [14]. However, high values have been detected in ex-smokers with chronic airflow obstruction. This fact would indicate that, in addition to active smoking, the oxidative stress of COPD contributes to the high levels of exhaled CO [15]. Similarly, an increase has been observed in the exhaled pentane and ethane figures in smokers without COPD. This converts these into biological markers of exposure to tobacco smoke, as well as oxidative stress which is generated in the airways [16].

Therefore, there is sufficient evidence to affirm that exposure to tobacco smoke is a risk factor for the development of respiratory pathologies (Table 2). Furthermore, genetic studies have confirmed that smoking interacts with asthma susceptibility genes [17].

Table 2 Smoking and its respiratory effects

Abnormal pulmonary functions [9]	**Abnormal biochemical functions**
Increased incidence of upper tract infections	Reduced production of endothelin 1 [11]
Increased incidence of lower tract infections	Increased NFκβ and apoprotein 1 [12]
Chronic cough	Increased interleukins 6 and 8 and TNF-α [13]
Exercise-responsive bronchospasm	Increase of exhaled CO due to increased heme oxygenase activity [14]

3. Treatments and success rates

The prevalence and economic impact of respiratory pathologies are a tremendous challenge for the public health worldwide. Programmes for the management and prevention of tobacco use must be developed to combat this burden. And the tendencies of smokers must try to be reversed with the use of available pharmacological treatments [18].

Melzer et al. [19] showed that patients with respiratory pathologies can respond equally or better to interventional treatments for smoking. However, some patients with severe respiratory pathologies continued to smoke and were unable (or unwilling) to stop smoking. The combination of medical advice and medication can lead to significant improvements in the smoking cessation rate.

Reducing the population's tobacco consumption should be a primary objective in professional organisations. In addition, a high quality of care is essential for all patients, especially those with respiratory pathologies. Although the treatments currently used in the clinic are, for the most part, cost-effective, improvements in existing cessation treatments are necessary [20].

The pharmacological treatments available in Spain are: nicotine replacement therapy (NRT) (patches, chewing gum, tablets or oral sprays), whose objective is the supply of decreasing doses of nicotine; bupropion, an atypical antidepressant that is considered first line for withdrawal, although its use is limited due to the risk of interactions with multiple drugs; varenicline, which acts as a partial agonist of nicotinic receptors, relieving the withdrawal syndrome by reducing the reward associated with use by blocking the receptor [21]; and cytisine, which binds predominantly to the α4β2 receptor, a nicotinic acetylcholine receptor subtype that lowers, at least partially, the rewarding and reinforcing effects of nicotine [22].

In addition, an assessment by the doctor is very important to be able to direct behavioural therapy with the aim of not only achieving cessation, but above all maintaining it [23]. It has been shown that the combination of professional advice with pharmacological treatment is more effective than either of them individually [21].

However, there exist a number of patients who do not stop smoking, either because they have not been able to or are not willing to quit.

The EDADES 2019/2020 survey [2] in 2019 revealed that the percentage of the general population between 18 and 65 years of age who do not consider smoking cessation is 40.5% in men and 36.8% in women. These percentages were higher than in 2017 (35.2% and 31.1% respectively; Figure 1). Due to these data, experts look for other ways or strategies to achieve smoking cessation or, at least, reduce the damage caused by its use.

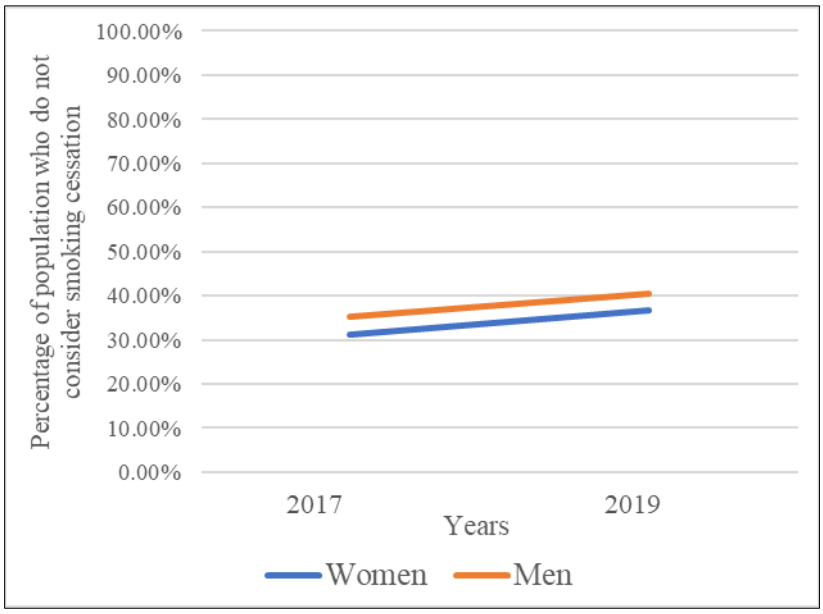


Figure 1 Percentage of smokers who do not consider quitting according to the EDADES 2019 survey [2]

4. New options/emerging strategies

Emerging strategies which are shown as alternatives to traditional cigarette use and that could be presented as an option to reduce, at least partially, the harm caused by tobacco are electronic cigarettes (EC) and heated tobacco products (HTP).

In these cases, the harm is reduced due to the temperature difference during tobacco use, as there is no combustion of organic matter, as occurs in the burning process with the conventional cigarette. However, the HTPs heat the tobacco preparation which produces the release of nicotine, giving the needed satisfaction to the user. These results make it an alternative strategy [24] without causing the combustion of tobacco, without generating smoke, and achieving a reduction in the potentially carcinogenic toxins that are present in tobacco smoke [25].

4.1. Electronic cigarette

Bhatta et al [26], in a randomised longitudinal study, showed the variation in the probability of developing respiratory pathologies with the use of ECs compared to the conventional cigarette. A 42% reduction of the obtained probabilities was calculated when the change from the use of the conventional cigarette (CC) to the EC was made. Substantial differences in the proteins expressed in the airway lung epithelial cells of smokers and EC users indicate that they both pose different independent risks. Finally, the respiratory incidents occurred prior to the market entry of the ECs. This observation suggests that the cases of respiratory diseases are not due to the inclusion of ECs as an alternative to conventional cigarette use.

Regarding the potential to use ECs as a tool to quit smoking, certain individuals find these devices more effective than NRT. Even so, more long-term scientific evidence must still be generated to confirm that they are really safer than conventional cigarettes [27]. However, it is reasonable to think that theoretically there is an absence of combustion and, therefore, a radical reduction of the toxic substances generated in that combustion. A one-year study randomised 300 smokers to three different combinations of EC with more or less nicotine (group A and B), including an arm without it (group C). Once the study ended, excluding those who quit smoking, 23% of the subjects in groups A and B and 4% of those in group C had a reduction of at least 50% of cigarettes per day in the use of tobacco. The percentage of patients who managed to quit smoking at the end of the study was 11% in groups A and B and 4% in group C. However, the reduction in the number of cigarettes per day and the levels of exhaled carbon monoxide were not significantly different between the three study arms, including the nicotine-free arm [28].

A review of 61 studies with a total of 16,759 patients has recently been published. This review shows, with moderate-certainty evidence, that quit rates were higher in the population randomised to nicotine EC than in those randomised to NRT (RR 1.53, 95% CI 1.21-1.93). These rates were also higher compared to patients randomised to non-nicotine EC

(RR 1.94, 95% CI 1.21-3.13). This review did not detect evidence of harm, represented by the presence of adverse effects, in the subjects of the nicotine EC group, but the longest follow-up was 2 years [29].

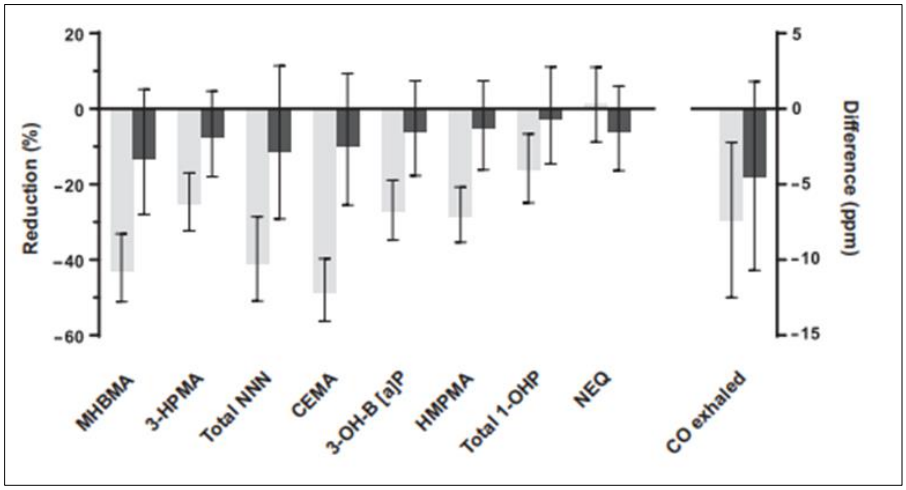
The study by Polosa et al [30] analysed the health effects in patients with COPD 12 months and 24 months after switching to ECs, and it showed that ECs can help the reduction in conventional cigarette use and aid in attaining continued abstinence. A significant reduction in respiratory pathology exacerbations in EC users compared to users of conventional cigarettes was observed. This exacerbation rate fell from a mean of 2.3 to 1.4 at 2 years, with reductions also being observed even in dual-user patients. Symptoms and physical activities tolerance improved at both visits compared to the control group, in which no change was observed. These data represented both objective and subjective improvement in COPD patients.

Undoubtedly, more long-term and comparative studies are needed to evaluate the efficacy of ECs versus NRT in smoking cessation. Likewise, studies on the long-term safety of ECs are required before conclusively establishing their usefulness as effective tools for smoking cessation. However, an important fact to note is that institutions such as the *Public Health England* of the United Kingdom maintain that ECs, alone or in combination with other methods, appear to be useful in reducing tobacco consumption in the short term [31]. In fact, the English Medicines and Healthcare Products Regulatory Agency (MHRA) is updating the clinical practice guidelines to include the possibility of prescribing electronic cigarettes to tobacco smokers who want to quit smoking, being the first country in the world to do so [32].

4.2. Heated tobacco

Another alternative to conventional cigarettes are HTPs. In these devices, the tobacco is heated up to 350°C without reaching combustion. This process produces a 90-95% reduction in the release of potentially dangerous and toxic components present in conventional cigarette smoke.

A study conducted in Japan to assess exposure to toxic substances of tobacco smoke with a 3-month follow-up, distributed the randomised participants into three arms: those who switched to HTP use, those who continued to use CC, and those who abstained from smoking. The results showed a significant reduction in 15 biomarkers of exposure and 15 harmful constituents present in conventional cigarette smoke. This reduction was comparable to the decrease in the same biomarkers for participants who quit smoking during the study [33].



MHBMA: 1,3-butadiene; 3-HPMA: crotonaldehyde; Total NNN: N-nitrosonornicotine; CEMA: acrylonitrile; 3-OH-BaP: benzopyrene; HMPMA: acrolein; Total 1-OHP: pyrene; exhaled CO: exhaled carbon monoxide. NEQ: nicotine equivalents; CC; conventional cigarette

Figure 2 Reduction of toxic substance exposure biomarkers [34]

These changes in the exposure to toxic substances were corroborated in another subsequent study in which the follow-up was 6 months (Figure 2) [34]. This study looked at other types of surrogate disease markers, high-density lipoprotein (HDL), white blood cell count, forced expiratory volume (FEV), carboxyhaemoglobin (COHb), total N-nitrosonornicotine (Total NNN), soluble intracellular adhesion molecule 1 (sICAM-1), 11 dehydro-thromboxane B2 (11-DTX-B2), 8-epi-prostaglandin F2 alpha (8-epi-PGF2α), with the majority of them showing a clear improvement compared to the group of smokers who continued with conventional cigarettes. A 6-month extension of the aforementioned study confirmed this improvement of the parameters compared to the arm that continued with the conventional cigarette [35].

Although the best option is smoking cessation, maintenance of the change in tobacco consumption shows a conservation of the reduction in biomarkers over time, indicating a potential reduction in tobacco-related diseases [36].

Cessation therapies have limited success in maintaining abstinence over time in smokers with COPD [37]. For this reason, although not completely risk-free, these new alternatives can produce clinically relevant changes in the health of those patients who manage to quit smoking [38]. For this, Polosa et al. conducted a study with the aim of assessing both objective and subjective health parameters in a cohort of COPD patients for 3 years, who had changed their consumption to HTP. The results showed that about 60% of COPD patients who used HTP completely abstained from conventional cigarette use for the duration of the study. In the case of dual-use smokers, a decrease in daily cigarette consumption of at least 70% was observed [39]. These results can be explained by the fact that the change in consumption to these products is similar to the experience of consuming a conventional cigarette and, therefore, could provide acceptable physical and behavioural reward effects [40]. Improvements in general health and physical activity were seen in COPD patients who stopped or significantly reduced their use of conventional cigarettes. This increase in health was reflected in a decrease in the mean number of exacerbations from 2.2 observed at the beginning of the study to 1.3 with the change to the use of HTPs. Likewise, improvements were perceived in the CAT score (COPD Assessment Test self-administered by patient) and the 6MWD test (to assess exercise tolerance) compared to the control arm of the study, which continued with conventional cigarette consumption. No variation at all was seen in the latter group [39]. These changes in the different variables are similar to those achieved through intensive detoxification programmes [41]. It is noteworthy that improvements in the CAT score were also observed in the case of dual-use smokers [39].

Finally, the work of Sharman et al [42] is the first observational longitudinal study of cohorts that has been conducted with the aim of demonstrating that switching from conventional cigarette consumption to HTP reduces the development and progression of COPD. The study data is being obtained from CT scans and respiratory function or spirometry tests. It started in 2017 with a participation of 1,200 participants, with an estimated completion date of 2023. Thanks to this study, it will be possible to know the effects of these devices in the long term and compare the results with those obtained in the short-term studies.

Altogether this collection of evidence has prompted regulatory authorities such as the FDA to authorise the marketing of one of the HTP products within the Modified Risk Tobacco Product category [43], once it was proved that it produced less exposure to toxic substances. This opens a new door for other public organisations to consider their position on these products. In this way, it is possible to achieve, protect and promote a health benefit for those patients who, having not been able to quit smoking, continue with tobacco consumption.

5. Conclusion

Smoking is the leading cause of morbidity and mortality worldwide and exposure to tobacco smoke is a risk factor in the development of respiratory pathology. There is a significant volume of patients who cannot or do not want to quit smoking and in whom pharmacological treatment and behavioural therapy have not achieved smoking cessation. In this sense, the possibility of supplying nicotine without combustion arises, through the use of devices such as electronic cigarettes and heated tobacco, which may constitute a less toxic alternative to the use of traditional combustion cigarettes.

The reduction of harm from the use of these new alternatives lies in the absence of tobacco combustion, leading to a decrease in the toxic substances present in tobacco smoke. There is scientific data that has determined that the use of HTPs and ECs decrease exacerbations of COPD and biomarkers of exposure. These observations have led institutions such as the *Public Health England* or the FDA to recognise the usefulness of these devices in reducing tobacco use in the short term. Therefore, they have been classified as risk-modifying products by these organisms because they cause less exposure to toxic substances.

However, long-term research is needed on the effects that these new alternatives cause on the health of consumers. Additionally, in situations in which the patient is not able to quit smoking, he or she should be informed about the improvements that occur when the pattern of consumption shifts from CC towards these alternatives. This information should focus mainly on the reduction of clinical biomarkers associated with smoking-related diseases, such as respiratory pathologies.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no competing interests.

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Authors' contributions

All the authors have jointly and equally contributed to the argumentation and writing of the paper.

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