Haut Conseil de la santé publique

Part of the report

on the benefits-risks of e-cigarettes

26 novembre 2021

A part of the report containing the main conclusions and recommendations is translated into English. ***This translation is given as an indication and only the full report in French is valid.***

The High Council of Public Health (HCSP) was referred by the Directorate General of Health (DGS) and the Interministerial Mission for the Fight against Drugs and Addictive Behaviors MILDECA on May 15, 2020 to update again its report of April 22, 2014, on the benefits-risks of e-cigarettes extended in the general population, updated a first time on February 22, 2016[1].

In the 2016 update, the HCSP had considered that:

- the electronic cigarette can be considered as an aid to smoking cessation for smoking populations wishing to stop smoking;

- is a tool for reducing the risks of smoking (with a question on concurrent users of tobacco and electronic cigarette);

- could be a gateway to smoking.

The HCSP had recommended:

- to continue and intensify policies against tobacco consumption;

- to inform, without advertising, health professionals and smokers that the electronic cigarette: is a tool to help stop smoking in populations wishing to get out of smoking; appears to be a mode of reducing the risks of tobacco in exclusive use. The advantages and disadvantages must be highlighted;

- to maintain the sales and advertising bans provided for in the law on the modernization of our health system and to extend the ban on use to all places designated for collective use.

Changes in the scientific, epidemiological, health and legal contexts justify an update of this statement.

[1] HCSP. Bénéfices-risques de la cigarette électronique pour la population générale [Internet]. Paris: Haut Conseil de la Santé Publique; 2016 Feb [cited 2021 Nov 17]. Available from: https://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=541

An ad hoc working group (WG) was set up in accordance with HCSP procedures (composition in Annex 2).

To answer the evaluation questions, the WG relied on

1. a research and literature review

2. written contributions from various stakeholders (list in Annex 4) according to an indicative framework.

The objective of the literature search was to complete the NASEM report (National Academies of Sciences, Engineering, and Medicine, United States), (bibliography until 30/8/2017) with the articles published since this research[2]. Also this NASEM report was taken as reference, for the literature prior to its publication. The literature review was carried out with the support of the company Cisame under a public contract, it covered the period 2017/2020. The WG completed this bibliography by a literature survey during the year 2021, until the date of submission of the statement.

CONCLUSIONS

Is vaping a smoking cessation aid? If so, what is its role in the smoking cessation strategy?

There is a strong assumption that electronic nicotine delivery systems (ENDS) could become first-line nicotine replacement therapies, but the number of trials is small and their methodological quality is below that recommended for such therapeutic trials.

No double-blind study comparing ENDS with electronic non-nicotine delivery systems (ENNDS) (without nicotine, considered as placebo) has shown superiority, i.e. a significant difference compared to placebo. The results of the ENDS with nicotine versus "advice" comparisons are unreliable, the comparisons to nicotine replacement therapy (NRT) are open (unblinded), therefore, these comparisons are potentially biased.

The collection of adverse events and serious adverse events is not systematic and poorly documented.

The last meta-analysis, Hartmann-Boyce et al. 2021b[3], shows a higher probability of smoking abstinence with ENDS than without nicotine (ENNDS) (4 studies) as well as a superiority of ENDS with nicotine versus NRT (3 studies). This meta-analysis only briefly reports the tolerance profile of ENDS due to the fact that tolerance profiles are poorly explored by individual studies.

[2] National Academies of Sciences, Engineering, and Medicine. 2018. *Public Health Consequences of E-Cigarettes*. Washington, DC: The National Academies Press.https://doi.org/10.17226/24952.

[3] Hartmann-Boyce J, McRobbie H, Butler AR, Lindson N, Bullen C, Begh R, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 2021 14;9:CD010216.

The publication of the systematic review and network meta-analysis by the Health Research Board of Ireland[4], an Irish government agency, predates the publication of Hartmann-Boyce et al. 2021b by 10 months[5]; it does not confirm any of the messages of the Cochrane meta-analysis (Harmann-Boyce et al. 2021b)]: no superiority of ENDS over ENNDS or NRT, and more adverse effects with ENDS than with ENNDS or NRT. It should be noted that this report could not include the Eisenberg et al. 2020 study[6] published later, which may have a decisive weight potentially explaining the major differences between these two main meta-analyses.

None of the studies reported here uses rigorous methodology such as that required for therapeutic trials in other therapeutic areas or for registration of health products in a therapeutic indication. This methodological deficiency results in uncertainty about the benefit/risk ratio of ENDS. For this reason, international guidelines do not recommend ENDS with or without nicotine as a therapeutic tool in the management of smoking cessation by health professionals.

Note: A national, multi-center, randomized, double placebo-controlled, therapeutic trial of the reference product (varenicline), the ECSMOKE study[7], which follows the recommendations of evidence-based medicine, is currently underway: A randomized, placebo-controlled, double-blind, multi-center trial comparing electronic cigarettes with nicotine to varenicline and electronic cigarettes without nicotine.

Is vaping an aid to smoking cessation in specific populations?

The literature does not allow us to find any randomized controlled trial conducted to date, comparing the use of a ENDS in smoking cessation to a ENNDS or to a pharmacological treatment to help smoking cessation in the specific population groups defined by the working group:

- Adolescent smokers
- Smokers with diseases associated with their tobacco use: cardiovascular, pulmonary and cancer diseases
- Smokers with psychiatric illnesses
- Smokers with co-addictions
- Smokers in precarious situations
- Pregnant smokers

Interventional, observational and prevalence studies of ENDS use in randomized trials have shown that:

- the use of a ENDS can allow to reach people with a high nicotine dependence and who do not access or do not wish to take pharmacological treatment for smoking cessation (patients with chronic

[4] Health Research Board. Electronic cigarette and smoking cessation. An evidence review [Internet]. 2020 [cited 2021 Nov 16]. Available from: https://www.hrb.ie/publications/publication/electronic-cigarette-and-smoking-cessation-an-evidence-review/returnPage/1/

[5] Hartmann-Boyce J, McRobbie H, Butler AR, Lindson N, Bullen C, Begh R, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 2021 14;9:CD010216.

[6] Eisenberg MJ, Hébert-Losier A, Windle SB, Greenspoon T, Brandys T, Fülöp T, et al. Effect of e-Cigarettes Plus Counseling vs Counseling Alone on Smoking Cessation: A Randomized Clinical Trial. JAMA. 2020 Nov 10;324(18):1844–54.

[7] the ECSMOKE trial protocol. https://bmjopen.bmj.com/content/9/5/e028832.info

obstructive pulmonary disease (COPD), patients with severe psychiatric illness, co-addictions in particular);

- acceptability and adherence to the use of a ENDS in some of these groups is particularly high and that ENDS could be used spontaneously as a complement to validated treatments.

In conclusion, a pragmatic approach must take into account that some smokers will prefer to use a ENDS rather than the health care system.

Can vaping be considered a tobacco risk reduction tool?

This question is complex and depends on the perspective: public health versus individual perspective for the general population of smokers or for specific populations of particularly vulnerable smokers.

It can be hypothesized that ENDS use alone is less risky than tobacco use but more risky than no use.

With this assumption, ENDS could represent a risk reduction tool in the following two situations:

- From a public health point of view, through a diversionary effect (use of ENDS as an alternative to tobacco use) and therefore a reduction in the incidence and prevalence of tobacco initiation and use among youth,

- From the individual point of view for smokers, by being a tool contributing to smoking cessation.

In the first situation, the strongest studies support a gateway effect rather than a diversionary effect. However, the levels of evidence are currently too low to allow a formal conclusion in one direction or the other.

In the second situation, two questions remain open; these are conditions for considering ENDS as risk reduction tools in tobacco smokers:

1) the efficacy of ENDS in terms of smoking cessation, and beyond efficacy the benefit-risk ratio compared to reference treatments (if the benefits are less and/or the risks greater than those of reference treatments, the use of ENDS as an alternative to these treatments constitutes a loss of chance);

2) the reduction of health risks with the short/medium/long-term use of ENDS as an alternative to tobacco remains hypothetical and has not been demonstrated in the absence of comparative short-, medium- and long-term data. However, it can be assumed that the overall risk is lower than the risk of continuing to smoke if one stops smoking tobacco and uses ENDS exclusively, and that the reduction in cigarette consumption associated with the use of ENDS, dual use or "vaping", does not modify the smoker's risk profile, and may even increase it (risk due to smoking plus the risk inherent in the use of ENDS).

However, half of the vapers continue to smoke occasionally or daily[8] .

[8] Andler R, Richard JB, Guignard R et al, Richard, J. Baisse de la prévalence du tabagisme quotidien parmi les adultes : résultats du Baromètre de Santé publique France 2018 [Internet]. Bull Epidémiol Hebd. 2019 [cited 2021 Nov 9]. Available from: http://beh.santepubliquefrance.fr/beh/2019/15/2019_15_1.html

In view of these elements, ENDS cannot at present be presented as a tool for reducing tobacco-related risks. An exception could be given: people who have a low acceptance of reference treatments (notably nicotine replacement therapy) and who conversely adhere to ENDS. This seems to be the case for certain vulnerable populations (see previous passage). It may also be the case in the general population due to individual preference. Thus, we can think that for a person who would not take any other treatment in the context of smoking cessation without ENDS, the use of ENDS could represent an opportunity versus the absence of treatment. As noted above, this is hypothetical and subject to the conditions listed.

Can vaping be a gateway to smoking for young non-smokers?

The scientific data are rather in favor of the initiating role of ENDS in tobacco consumption among adolescents. However, studies are not free of bias and to our knowledge, no cohort has been conducted in France to answer this question.

In 2016, the report of the HCSP[9] indicated that "(...) the electronic cigarette (...) could constitute a gateway to smoking. This risk would be counterbalanced by the fact that the electronic cigarette could delay the entry into smoking".

The NAS synthesis[10] and the complementary bibliography carried out by the HCSP do not allow to question the first proposal ("could constitute a gateway to smoking"). The conditional used in 2016 is still relevant because of the methodological limitations of the studies and the questionable transposability of foreign results to the French context. On the other hand, the literature does not support the second proposition ("the electronic cigarette could delay the onset of smoking."), which was based at the time on the opinion of stakeholders.

Is there a risk that these products could promote a renormalization of tobacco consumption?

Currently, there is insufficient evidence to conclude categorically whether or not ENDS lead to renormalization of tobacco use. In particular, the primary indicator of renormalization (smoking prevalence and ENDS) indicates that, given the available data, while the relationship between ENDS initiation and smoking initiation is possible, it remains to be confirmed.

However, the research reviewed shows that the strong presence of ENDS in the environment and the marketing of these products (advertising, flavors, etc.) would have a positive influence on the perceptions and behaviors of youth and nonsmokers and would reduce the perception of the health risks of ENDS.

However, the research identified to address the renormalization question suffers from several limitations:

[9] HCSP. Bénéfices-risques de la cigarette électronique pour la population générale [Internet]. Paris: Haut Conseil de la Santé Publique; 2016 Feb [cited 2021 Nov 17]. Available from: https://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=541

[10] HCSP. Bénéfices-risques de la cigarette électronique pour la population générale [Internet]. Paris: Haut Conseil de la Santé Publique; 2016 Feb [cited 2021 Nov 17]. Available from: https://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=541

- very few longitudinal studies and randomized controlled trials (difficult to set up given the topic) have been established. Most studies are cross-sectional (sometimes with non-representative samples) and/or qualitative;

- Most studies have been conducted in the United States and Great Britain where the prevalence is low compared to France. Very few studies have been conducted in France;

- These studies were carried out at a time when ENDS had only recently arrived on the market. However, the evolution of a norm and a possible renormalization of tobacco takes time, as do changes in behavior.

RECOMMENDATIONS

In terms of the management of smokers

- **Recommendation 1**: Health professionals who support smokers in their efforts to quit smoking should use treatments, whether or not they involve medication, that have been proven effective. Evidence-based knowledge is insufficient to propose ENDS as smoking cessation aids in the management of smokers by health professionals.

- **Recommendation 2**: These products are consumer products and can therefore be used by the population outside of (or in addition to) treatment within the health care system. The absence of evidence-based knowledge does not exclude that the benefit/risk ratio of these products used outside the health care system may represent a help for some consumers and thus contribute to improve their health.

- **Recommendation** 3: The HCSP advises against the use of ENDS and ENNDS in pregnant smokers in the absence of data on efficacy, and as a precautionary principle in the absence of data on risks. There is an effective and proven safe alternative with NRT in the context of management by a health professional.

- Recommendation 4: The HCSP considers that ENDS could be used to reach vulnerable populations (due to co-addiction, co-morbidities, social factors...) with high nicotine dependence, having expressed a preference for ENDS and presenting a low adherence to validated treatments. The priority remains to improve their access to care and their management; in this context, validated treatments should be offered as first line. This recommendation is conditional on advice on safe use, and is temporary pending data from trials on the benefit-risk ratio in each of the populations concerned.

In terms of public policy

- **Recommendation 5:** The HCSP proposes the immediate implementation of a system for the collection of symptoms and health problems associated with the use of ENDS/ENNDS by the general public ("vapovigilance" system), via signalement.fr, with a standardized form. Any packaging of a ENDS or display (place of sale) should include information on this reporting system. The provisions of this vigilance system must allow for an analysis by specific population groups. In addition, all data from existing monitoring systems should be analyzed in a coordinated manner.

- **Recommendation 6**: The relationship between ENDS initiation and smoking initiation is documented by cohort studies. In addition, there are some safety signals about the risks associated with ENDS use (nicotine, other products) and about detour of use. The objective of delaying the initiation and use of ENDS among adolescents who do not use tobacco is therefore based on the precautionary principle. The HCSP recommends that the ban on sales to minors be maintained and that measures be taken to ensure the effectiveness and monitoring of its application.

- **Recommendation 7**: The HCSP recommends that all legislative and regulatory measures relating to ENDS be maintained in order to limit their attractiveness and accessibility, and that measures be taken to ensure their effective application (in particular, a ban on advertising, a ban on consumption in schools and establishments intended for the reception, training and accommodation of minors, means of transport, and workplaces, a ban on certain claims on packaging, and a ban on certain additives)

- Recommendations 8: Within the framework of public information, it is recommended to elaborate recommendations for the use of ENDS for the public based on the analyses in progress of ANSES (safety conditions, advice for temporary use, avoidance of "Do it yourself", etc.).

In terms of informing the population

- **Recommendation No. 9**: inform the population that

1) the potential benefits and risks of the medium or long-term use of electronic cigarettes with or without nicotine, are not established to date;

2) it is recommended in a process of smoking cessation, to seek the help of a health professional, and to use drugs and / or non-medicinal therapies that have proven their effectiveness;

3) if you use ENDS/electronic cigarettes as part of a cessation process and if they are well tolerated, it is important to stop smoking tobacco completely;

4) the ENDS association to tobacco is formally discouraged in all situations;

5) as a precautionary principle, it is recommended to avoid personal initiatives of "do it yourself" mixtures, in particular of substances not identified and not evaluated by Anses in the framework of its mission.

6) there is a system for reporting symptoms, diseases/health problems.

- Recommendation 10: The HCSP recommends that health education interventions aimed at young people on smoking include knowledgeable information on ENDS/electronic cigarettes.

In terms of research

- **Recommendation 11:** Therapeutic trials that comply with national and international methodological recommendations are needed to evaluate, with a sufficiently high level of evidence, the therapeutic efficacy and tolerability of ENDS in smoking cessation compared to placebo and/or reference treatments. This recommendation applies to the general population, and must also be applied to adolescents and to various vulnerable groups (due to co-addiction, comorbidities, social factors, etc.). These data must be completed by medium and long term cohort studies in order to measure long term consumption (withdrawal or not from ENDS, resumption or not of tobacco consumption...) as well as to compare the risks in terms of health between types of consumption.

- **Recommendation 12**: The scientific evidence supports a role for ENDS in smoking initiation. However, the available studies are not free of bias and to our knowledge no cohort study has been conducted in France to answer this question. It would thus be important to support the production of data in the French context on the relationship between ENDS initiation/consumption and tobacco initiation/consumption among adolescents. In order to answer this question, longitudinal cohort studies should be conducted, taking into account all individual and collective factors of tobacco initiation, providing precise measures of consumption that differentiate between experimentation and use, and controlling for the number of dropouts during follow-up.

- **Recommendation 13**: The French market offers a wide variety of flavors, some of which explicitly target youth. Some European countries have banned certain flavors and the WHO recommends that flavors be banned to reduce the attractiveness of these products to young people. In this context, the HCSP recommends the acquisition of knowledge on the attractiveness of flavors, taking into account practices in France.

These recommendations, based on the knowledge available at the date of publication of this report, may evolve according to the updating of knowledge and epidemiological data.