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The E-cigarette: Addressing patients' questions and physicians' doubts

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INTRODUCTION

Chronic tobacco consumption is the first worldwide cause of avoidable deaths. According to a report of the World Health Organization (WHO), in 2004 tobacco was responsible for 12% of the deaths of persons under 30 years old occurring throughout the world, and of 16% in Europe and the United States[1]. In 2010 in France, no less than 78000 deaths were attributable to tobacco[2]. The causes of these deaths were principally cancers (47000 deaths), cardiovascular diseases (20000 deaths) and respiratory diseases (11000 deaths)[2]. Given the many complications associated with tobacco consumption, health care professionals are called upon to 1) limit initial smoking, particularly in juvenile populations; 2) having identified and started to treat their tobacco addiction, help smokers to put an end to their tobacco consumption; 3) encourage risk reduction strategies for those who have continued smoking.

Understanding addiction to tobacco and its treatment

According to the *Baromètre santé* investigation, in 2016 34.5% of the French population ranging in age from 15 to 75 years smoked tobacco; 83% of the consumers were daily smokers[3]. In some cases, daily tobacco consumption is favored by an addiction mechanism, which is defined by ICD-10 and DSM-5 diagnostic criteria such as "repeated, compulsive use of tobacco despite its harmful effects"[4]. Indeed, repeated and continued use generates suffering in the smoker. The central symptom of addiction is the phenomenon of craving, which may be defined as the intense and irrepressible urge to use tobacco at the wrong time[5,6]. Indeed, craving is the clinical expression of the phenomenon of loss of control; its intensity is predictive of relapse. Some smokers are afraid of quitting or else, following repeated but fruitless attempts, no longer wish to do so (or have essentially "given up"). This is due to tobacco addiction, which thwarts the user in his attempts to control his consumption by rendering him defenseless against craving and relapse. Addiction is the element that indefinitely prolongs the smoker's chronic consumption of tobacco. Without therapeutic assistance, a mere 3 to 5% of smokers who attempt to quit manage to achieve prolonged tobacco cessation[7].

There exist a number of medications that efficaciously combat tobacco craving:

nicotine patches, varenicline and bupropion[8,9]. The risk-benefit balance of varenicline has been debated. Recent studies, however, suggest satisfactory safety from a cardiovascular and psychiatric standpoint as well as efficacy in the achievement of prolonged abstinence[8,10,11]. That much said, the results of one of these studies may be questionable due to a conflict of interest[11]. It also bears mentioning that the effects of anti-craving medication are increased when associated with psychological support[12].

The concept of risk and damage reduction (RDR)

The toxicity of tobacco use is essentially due not to addiction as such, but rather to the direct toxicity of smoke (tars, carbon monoxide or CO). As a result, it is at least theoretically possible, in cases of addiction, to reduce the damage due to tobacco use by quantitatively reducing, if not altogether eliminating, exposure to tobacco smoke. That is why an approach aimed at rendering tobacco less detrimental to the health of a smoker who does not stop smoking has been introduced; it is known as "risk and damage reduction" (RDR). Its guiding principle was first presented in 1974 by Michael Russell, who spoke at the time of "safer smoking, with realistic goals"[13]. RDR may be defined as recourse by a smoker to a less health-damaging alternative consisting in reduced consumption of combustible tobacco, without his having necessarily put a complete end to his use of tobacco or nicotine[14]. Unfortunately, the RDR strategy is perhaps bound to fail due to a titration mechanism. By reducing the number of cigarettes smoked, smokers "fine-tune" their way of smoking by inhaling more longly and deeply than previously, which leads to their exposing themselves to the same quantity of tar and CO as before[15]. In fact, the titration mechanism may even increase exposure to tobacco smoke!

As for the smoker who does not desire treatment for his tobacco addiction, nicotine in a non-smoked form can be of help from a RDR standpoint[9,16]. The number of cigarettes smoked and the quantity of inhaled smoke are reduced[14], the titration mechanism is limited, and a step toward total tobacco cessation may possibly be taken, especially in very heavy smokers[17-21].

In addition, appropriate utilization of available medications enhances the chances that a smoker will succeed, if not in avoiding all exposure to smoke, at least in having it significantly reduced. Medications targeting craving are often preferred by persons wishing to undergo treatment for their addiction. And for those who may be loath to accept a therapeutic approach, a wide array of nicotine replacement products possessing a psychotropic effect comparable to that of a cigarette (but without exposure to smoke) are frequently employed: chewing gum, sucking pastille/lozenge, sublingual tablet, inhaler, oral spray[5,9,12,13].

Effect of smoking reduction on health

A lessening pf morbi-mortality due to reduced tobacco consumption without cessation remains questionable. Smoking duration is far more detrimental to health than quantity smoked. While doubling daily tobacco consumption also doubles the risk of lung cancer, doubling the duration of tobacco consumption multiplies the risk by 2022! In 2006, Tverdal and Bjarveit evaluated mortality among 20-to-49-year-old Norwegians, smokers of at least 15 cigarettes a day and monitored for 3 to 13 years[23]. Compared to persons who had not modified their tobacco consumption, those who had stopped smoking during the follow-up period were at demonstrably reduced risk of death. Indeed, mortality diminution encompassed deaths due to cardiovascular disease, coronary disease, lung cancer and all causes. On the other hand, when tobacco consumption had decreased by less than 50%, improved survival was not observed. In 2012, however, Gerber *et al*. noted diminished overall mortality among daily Israeli smokers of at least 40 years of age who had reduced their tobacco consumption24. In yet another study, conducted in 2013 and involving 40-to-65-year-old Scotsmen monitored for more than eighteen years, reduced smoking was not associated with reduced mortality, whereas tobacco cessation decreased overall mortality and deaths due to non-cardiovascular diseases[25]. The systematic review by Pisinger and Godtfredsen published in 2007 revealed improved respiratory symptoms and diminished risk of lung cancer in cases of reduced tobacco consumption, which was nonetheless not associated with diminished risk of hospitalization for myocardial infarction or exacerbation of chronic obstructive bronchitis[26].

Tobacco addiction contributes to morbi-mortality attributable to chronic use. There exist efficacious anti-craving medications enabling durable suspension of tobacco use through remission of the addiction; they include patch, varenicline and bupropion. When total remission (abstinence) is not desired or not achieved, partial remission (reduced use) must no longer be conflated with failure. On the contrary, it should be valued as an intermediate step and sustained by nicotine replacement products of greater acceptability for the undecided smoker: chewing gum, sucking pastille/lozenge, sublingual tablet, inhaler or oral spray.

Functioning of the electronic cigarette

The electronic cigarette (or e-cigarette) was created in the early 2000s by a Chinese pharmacist, Hon Lik, who had the idea of using a piezoelectric ultrasound element to vaporize a nicotine solution in a device reminiscent of a cigarette. In China in 2009, a patent was granted for his technique of vaporization by heating resistance. The e-cigarette is a device diffusing the aerosol spray of a solution called e-liquid, which is composed of propylene glycol (PG), vegetable glycerin (VG), an aroma and, quite often, nicotine[27]. There exist different types of e-cigarettes (**Figure**). Schematically speaking, they all consist in a mouthpiece, an e-liquid chamber, a resistor (or atomizer), a vaping wick bringing the e-liquid into contact with the atomizer by capillary action, and a rechargeable battery. Their functioning is triggered by a microwave sensitive to inhalation or by a manual switch. The triggering mechanism induces power provisioning by the battery. Heating of the resistor converts the e-liquid into a gaseous state, so that it becomes an aerosol, the spray inhaled by the user, who is also known as the vaper. First-generation models resembled cigarettes, and were disposable. Second-generation models looked like pens, and were rechargeable. As for today's third-generation models ("mods"), power output can be modified by the vaper, the atomizers are of higher efficiency and user autonomy is greater (**Figure**). Different modulations enable variation of the heating temperature of the atomizer (temperature-controlled vaping), and consequently of the sensations experienced during inhalation as well as spray density. The most widely used models are second-generation and third-generation.

Propylene glycol (PG) serves as a humectant (a moisturizer) and a preservative in the agri-food industry, in the pharmaceutical industry and in cosmetology. Vegetable glycerin (VG) is a commonly used food and drug additive[27]. In e-liquid, PG and VG serve as flavor enhancers and help to produce a "vapor" effect[27]. PG tends to irritate the respiratory airways, and also occasions throat irritation and coughing. However, PG is also the e-liquid ingredient that at once heightens flavors and provokes the "throat hit" effect, which may be defined as a tingling at the back of the throat experienced when taking a puff on a cigarette or inhaling the e-liquid spray. As for VG, it increases vapor density. To reduce irritant effect, a vaper can diminish the proportion of PG, thereby increasing the proportion of VG in the e-liquid. This can be done by verifying the PG/VG ratio in the e-liquids purchased, or else by producing them oneself. A heightened proportion of VG can render the vapor more dense and abundant, thereby fulfilling the desire of some vapers; on the other hand, it may attenuate "throat hit" and flavor perception. And since VG is viscous, the atomizer is rapidly dirtied and clogged due to repeated contact. And so, when the vaper has chosen to use e-liquids with highly concentrated VG, he must buy an atomizer adapted to viscosity or at least make sure that his e-cigarette is fully compatible with this type of e-liquid. At times, an e-liquid may contain a small quantity of alcohol and/or water that will facilitate aroma dilution[27]. When nicotine is present, is has been extracted from tobacco plants, and its extraction may produce trace impurities such as anatabine or anabasine, which present no health risk[27,28], as well as residues of the pesticides used in tobacco crops.

The prices of e-cigarettes and refills are variable. Second and third-generation devices may cost from 20 to 150 euros. A 10 mL flask of e-liquid is sold at a price of 5 to 8 euros. Wear and tear necessitate frequent changes of atomizer, resistor and battery. Two e-liquid flasks will generally be used during a typical week, but the exact number will vary according to the frequency and intensity of inhalation, the sensations desired, the nicotine content, etc. That said, daily smokers have reported that on the average and over the long term, e-smoking is five times less expensive than smoking. In a 2010 on-line study of e-smokers, most of whom wished to stop

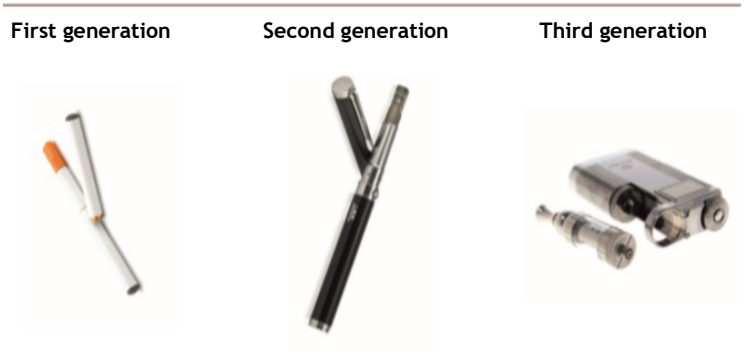

Figure - Examples of electronic cigarettes
Source : Farsalinos KE, Polosa R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. Ther Adv Drug Saf 2014;5:6786

smoking, e-cigarette use was found to cost approximately 27 euros a month (purchase of material included), whereas their regular smoking of a pack a day of tobacco had cost them about 165 euros a month[29].

For smokers, vaping could represent a means of inhaling nicotine that would reproduce smokers' characteristic gestures yet be less detrimental to their health. Social and researcher interest in this instrument and its use has steadily grown[30-32]. Given the singularity of their missions and their presence throughout the territory, general practitioners are more often than not the medical professionals most likely to repeatedly meet smokers over the course of their lives. Given their status as providers of primary care, they carry out tasks of prevention, health promotion and monitoring over the long term, and it in this context that they may be called upon to give advice to their patients on the e-cigarette. It consequently seemed necessary to furnish a situational analysis addressing the questions currently put forward by general practitioners: How pervasive is the phenomenon? What is the existing regulatory framework? What are the profiles of typical users? Is the e-cigarette an effective tool, likely to reduce smoking and perhaps facilitate tobacco cessation? What, on the contrary, are its adverse effects and health risks? What kinds of studies might help, in the future, to improve our knowledge and enhance our understanding?

PREVALENCES OF USE

According to the results of the *Eurobaromètre 2017* survey, 15% of Europeans had tried the e-cigarette and 2% were engaged in e-smoking at the time of the investigation. Two thirds of current vapers were daily vapers. Between 2014 and 2017 e-cigarette experimentation grew by 12 to 15%; as of now, the proportion has stabilized.

The definitions of e-cigarette use applied in the Eurobaromètre (Europe) and Baromètre santé (France) surveys.

Experimenters: Those who have tried at least once in their lives to utilize an e-cigarette.
Current users: Those who have tried the e-cigarette and were still utilizing it, daily or occasionally, at the time of the survey.
Vapo-smokers (dual users): Those concomitantly utilizing tobacco and e-cigarettes at the time of the survey.

In France, e-cigarette experimentation currently approximates 24 to 25%[3,33]. It involves 54.4% of smokers and 8.9% of non-smokers. The extent of e-cigarette experimentation seems higher in France than in the rest of Europe. France also appears to present the second most substantial proportion, after the United Kingdom, of current e-smokers, 4 and 5% respectively. Compared to the rest of Europe, between 2014 and 2016 the extent of e-cigarette experimentation in France was at once considerable and stable. On the other hand, while the extent of daily e-cigarette use in France had declined, from 2.9 to 2.5%, it remained among the highest in Europe[3,33].

REGULATORY FRAMEWORK

In France, e-cigarettes and their refills are neither tobacco -derived products nor as medications. They are rather considered as current consumer goods corresponding to "*the general safety requirement in accordance with the provisions of the Consumer Code*"[34].

Subsequent to adoption of European directive 2014/40/UE35, the promotion, sales and use of these products are regulated as follows:
- Not having received marketing authorization (MA), they cannot be sold in pharmacies and are not registered in the list of articles approved for medical purposes by order of the French health ministry[34];
- The sale or offering of e-cigarettes to minors is forbidden[36];
- Advertising for the electronic devices and their refills is authorized only in the establishments where they are sold[37,38];
- Since 1 October 2017, e-cigarette use has been prohibited in establishments dedicated to the hosting, training, and accommodation of minors; in enclosed means of public transportation (buses, trains, subways); and in enclosed group workplaces (shared offices)[39]. Persons in non-compliance with this rule are subject to a fine. On the other hand, e-cigarettes are not prohibited in individual offices and in places open to the public, except when expressly forbidden by the internal regulations of a given establishment.

VAPERS' CHARACTERISTICS AND EXPERIENCES

E-smoking is particularly favored by current smokers, former smokers and young people[3,28,32,40-46]. In 2016 in France, 41% of vapers were former smokers and 48% were daily smokers[3]. Compared to exclusive cigarette smokers, according to the results of different studies vapers seem to have

Authors and year of publication	Country	Study method	Participants	Total follow-up duration (months)	Study endpoints
Bullen *et al.* 2013	New Zealand	Randomized controlled superiority trial with 3 parallel arms	Adult smokers (at least 10 cig/d), wishing to stop smoking (n = 657)	6	Cessation (for 6 months) and reduction of smoking (in number of cig/d)
Caponnetto *et al.* 2013	Italy	Randomized controlled superiority trial with 3 parallel arms	Adult smokers (at least 10 cig/d), not wishing to stop smoking (n = 300)	12	Cessation and reduction (by at least 50%) of smoking
Vickerman *et al.* 2013	United States	Cross-sectional study	Adult smokers participating in a smoking cessation program (n = 2758)	7	Smoking cessation (at least 1 month)
Grana *et al.* 2014	United States	Prospective study	Adult smokers (n = 949)	12	Cessation and reduction of smoking (in number of cig/d)
Polosa *et al.* 2014	Italy	Prospective study	Adult smokers (at least 15 cig/d over at least 10 years), not wishing to stop smoking (n = 50)	24 (preliminary e-cigarette phase over the first 6 months)	Cessation (at least 1 month) and reduction (at least 50%) of smoking
Biener *et al.* 2015	United States	Prospective study	Adult smokers (n = 695)	36	Smoking cessation (at least 1 month)
Brose *et al.* 2015	United Kingdom	Prospective study	Adult smokers (n = 1759)	12	Cessation and reduction (by at least 50 %) of smoking, attempt to quit (cessation at least 24 h)
Hitchman *et al.* 2015	United Kingdom	Prospective study	Adult smokers (n = 1 643)	12	Smoking cessation
Manzoli *et al.* 2015	Italy	Prospective study	Daily smokers, adults (n = 959)	12	Cessation (at least 1 month) and reduction of smoking (in number of cig/d)
Pearson *et al.* 2015	United States	Data extracted from a clinical trial	Adult smokers (n = 2 123)	3	Cessation (at least 1 month) and reduction of smoking (in number of cig/d), attempt to quit
Manzoli *et al.* 2017	Italy	Prospective study	Daily smokers, adults (n = 932)	24	Cessation (at least 1 month) and smoking reduction in number of cig/d and reduction by at least 50%)
Zhu *et al.* 2017	United States	Combined data from 5 studies, from 2001 to 2015	Daily smokers, adults (n = 23270)	12	Smoking cessation (at least 3 months), attempt to quit (at least 24 hours)
Pasquereau *et al.* 2017	France	Prospective study	Smokers aged 15 to 85 years (n = 2057)	6	Smoking reduction (at least 50 %), attempt to quit (at least 7 days)

Table - Summary of the studies having evaluated the efficacy of the e-cigarette in cessation or reduction of smoking and in attempts to quit

They may also have a more clearly defined intention and a more pronounced motivation to stop smoking[47-49]. Indeed, the most frequently reported motivation for initiation to vaping is tobacco cessation or reduction. The other reasons for which smokers engage in e-cigarette experimentation include: curiosity, lower cost or lesser harmfulness, reduction of second-hand smoking, permissibility of vaping in areas where smoking is prohibited[29,32,41,43,47,50,51].

Many vapers had tried various medications with tobacco cessation indications before using the e-cigarette. For them, nicotine replacements have been identified as medications intended for persons wishing to stop smoking. However, in the different studies the role they ascribe to the e-cigarette is more ambiguous; it could be seen either as an alternative to tobacco or as an instruments at their disposal in their attempts to quit. Other e-smokers have described the e-cigarette as a way of giving up tobacco without giving up nicotine; while they had managed to stop smoking, they had no desire to stop vaping. Their reasons included: an agreeable experience of vaping and the feeling that there was no rush[50,52,53]. Continued use of the e-cigarette subsequent to initiation was favored by the following factors: the agreeable effects experienced during vaping; a feeling of personal efficacy reinforced by durable achievement of tobacco reduction or cessation thanks to the e-cigarette; the socially favorable image of vaping, in comparison with smoking; the feeling that vaping was less harmful; the sense of belonging to a community[50-54]. Some e-smokers mentioned what they experienced as the lower efficacy and more numerous adverse effects of anti-craving medications in comparison with e-cigarettes[52-55]. They also considered the e-cigarette as a tool allowing them to end their tobacco consumption while exerting less effort and encountering less frustration than with nicotine replacement products.

EFFECTIVENESS OF THE E-CIGARETTE

Vapers have reported on experimenting with the e-cigarette so as to stop smoking and have described it as an effective tool in tobacco cessation or reduction. However, its efficacy has not been clearly established in studies on the subject, of which the characteristics are summarized in the **Table**.

Total tobacco cessation

To our knowledge, up until now only two randomized controlled clinical trials, both of them published in 2013, have evaluated the effect of e-cigarettes with nicotine vs. e-cigarettes without nicotine in the perspective of prolonged tobacco cessation[56,57]. The first trial was carried out in Italy and included 300 smokers who did not wish to stop smoking and utilized e-cigarettes with or without nicotine (placebo group)[56]. The proportion of smokers in the total sample durably abstaining from tobacco 40 weeks after the end of the intervention was 8.7%. There was no significant difference between the two groups. The second trial included 657 New Zealand smokers wishing to stop smoking and divided into three groups: e-cigarette with nicotine, e-cigarette without nicotine (placebo) and nicotine patches[57]. The proportions of smokers abstaining from tobacco during six months were 7.3%, 4.1% and 5.8% respectively, without any statistically significant difference. Several factors could help to explain why no evidence of effectiveness was displayed in these studies: short duration of treatment (3 months of intervention in the two trials); the nicotine dosages in the e-liquids used (low doses remaining the same throughout the intervention); the fact that a) possible support for attempts to quit and; b) use of first-generation e-cigarettes were not taken into account. Given these limitations, we cannot presently draw conclusions on the questions put forward in the two studies.

Longitudinal observational studies have likewise dwelt on a possible association between vaping and tobacco cessation in smokers (**Table**). At 3, 7, 12, 24 or 36 months of follow-up, they compared proportions of tobacco cessation in vapers vs. non-vapers[58-66]. Some of these studies have reported higher proportions of tobacco cessation among vapers[59-64]. In two of them, there was an association between frequency of e-cigarette use and chances of achieving cessation[61,63]; daily vapers were more likely to durably stop smoking after 12 or 36 months of follow-up. In other studies, no significant association was found between e-cigarette use and tobacco cessation58,65,66. The different meta-analyses evaluating this endpoint have presented contradictory results[67-69].

Some pilot studies have suggested that e-cigarettes with a nicotine-containing e-liquid may be more effective than a placebo in attenuating the physical signs of weaning and lessening the urge to smoke during the early phases of tobacco cessation. Relief from weaning symptoms appears

greater in the second-generation compared with the first-generation devices[70,71].

Tobacco reduction

The effect of the e-cigarette on reduction of tobacco consumption was also evaluated in the two previously cited clinical trials. In one of them, there was no statistically significant difference in terms of diminution of the number of cigarettes smoked between the vapo-smokers and a placebo group at 3, 6 and at 12 months[56]. In the second trial, a significantly higher number of users of nicotine-containing e-cigarettes than of smokers with nicotine patches reduced their smoking by at least 50% in 6 months 57% vs. 45% (p = 0.0857). Several longitudinal studies on tobacco reduction have monitored smokers for 6, 12 or 24 months[49,60,62,65] (**Table**). In some of these studies, provided that dual use was not prolonged indefinitely, e-smoking increased the likelihood of reduced tobacco consumption by at least 50% at 12 or 24 months[60,62]. In 2015, Brose *et al*. reported diminution of tobacco consumption equaling or exceeding 50% only in persons who were daily e-smokers at baseline. Compared to the non-vapers, likelihood of cutting down by at least 50% the number of cigarettes smoked per day was higher among the daily vapers: adjusted odds ratio = 4.19 [CI95 = 2.13-8.24][65].

Lastly, in the study conducted in 2014 by Pasquereau *et al*. on a panel of French smokers, at 6 months reduction of tobacco consumption by at least 50% had occurred more often in e-smokers than in persons smoking tobacco only. That much said, this diminution of smoking by at least 50% was significant only in smokers with an elevated dependence score on the Heaviness of Smoking Index (HSI)[49].

Number of attempts to quit

Several longitudinal studies have compared, vapers vs. non-vapers, the number of smokers' attempts to quit at 3, 6 and 12 months[47,56,62,63] (**Table**). In all of these studies , e-cigarette use was shown to increase the number of attempts to quit. In the study by Brose *et al*., daily vapers more frequently attempted to quit than non-vapers, while the number of attempts to quit by occasional vapers and non-vapers was statistically equivalent[65].

Vapers have reported on their using e-cigarettes to reduce their smoking and, at times, to quit. The effectiveness of the e-cigarette in tobacco diminution or cessation has not been clearly established in the published studies. That said, in the medium term e-cigarette use could be favorable to attempts to end or reduce tobacco consumption, particularly among daily e-smokers and those who do not engage in prolonged dual use. As of now it has not been demonstrated that vaping is propitious to successful attempts at tobacco cessation.

Sidebar 3

E- SMOKING: THE ASSOCIATED RISKS

Toxic effects

When placed in contact with human as well as animal cells in studies *in vitro*, e-liquids were found to be toxic[72-78]. Their cytotoxicity, which was nonetheless less than that reported for tobacco, may be partially due to aromas, particularly cinnamon and tobacco[72-74].

The 2016 study by Allen *et al*. documented the presence of diacetyl in e-liquids79. Diacetyl is an additive utilized in the agro-food industry to imbue foods with the taste of butter or cheese; in e-liquids, it is added so as to reinforce the sweet, sugary flavors. Prolonged inhalation and/or high dosage is associated with rare yet severe *bronchiolitis obliterans*, also known as fixed obstructive lung disease or "popcorn lung", an occupational hazard at plants that manufacture flavorings80. As for acrolein, it is derived from VG dehydration occurring when the latter is heated at a very high temperature (>280°C)[27]. This happens, for example, when the wick of certain models undergoes heating without having been adequately impregnated with e-liquid. Acrolein is cytotoxic, irritating for the skin and the mucous membranes. When it is produced, the user not only perceives a pungent off-flavor, but is also subject to signs of irritation of the upper aero-digestive tract[27]. Since 2015, the standards applied by the *Association française de normalisation* (AFNOR) have imposed limits on the risks generated by e-liquids manufactured in France. However, the subsisting risks are far from negligible inasmuch as vapers can easily carry out on-line purchases of products manufactured outside of "the Hexagon". Moreover, in a do-it-yourself (DIY) spirit, some vapers concoct their own e-liquid, and the health-damaging effects of the inhalation of aromas combined by these users are totally unknown. Last but not least, AFNOR standards are anything but mandatory for manufacturers, vendors or marketers of e-cigarettes and their refills. Even though applied by

most of these actors, the standards remain recommendations, and consequently cannot be legally enforced.

A 2012 experimental study by McAuley *et al*. on concentrations in the air of toxic compounds showed that tobacco smoking produced more volatile organic compounds, carbonyl compounds, nitrosamines and small particulates than e-liquid sprays[81], and the study by Goniewicz *et al*. yielded similar results. However, in 2013 another American study found traces of metallic nanoparticles in the air after e-cigarette use at concentrations equal to or higher than those found in tobacco smoke[78]. In fact, metallic particles in e-liquid are associated with its receptacles; when the latter are metallic, the particles are inevitably present in the liquid, and they have also been found in spray from the Nicorette® inhaler[82]. And yet, at least for the time being, concentrations of metallic particles detected in the spray produced during e-smoking do not seem relevant in terms of clinical repercussions. It nonetheless bears mentioning that in all these cases, the presence of nanoparticles (even at trace levels) and of potentially health -damaging aromas (when inhaled) raises the question of the need to apply more rigorous quality controls to the manufacture of e-cigarettes and their refills.

Goniewicz *et al*. have evaluated the urinary excretion of nicotine metabolites and of substances reputedly toxic in humans[83]. They asked 20 daily smokers having the intention to stop smoking to make use of an e-cigarette for two weeks. While being monitored, they totally or partially replaced their tobacco consumption by the e-cigarette. The substitution was marked by a significant reduction in their urines of the biomarkers for nitrasamines, benzine, 1,3-Butadiene and ethylene oxide. Diminution was more frequently found in the 9 persons in the study having totally stopped smoking than in the 11 persons having only reduced their consumption[83]. Hecht *et al*. reported similar results[84].

Health-damaging effects

Experimental models involving cells or animals are not necessarily predictive of the impact of e-liquid spray on human beings. The dangerousness of smoked tobacco is primarily explained by the production of CO and tars during combustion. Due to its being devoid of combustion, even the prolonged and intense use of e-cigarettes is far less health-damaging than prolonged consumption of smoked tobacco.

The most frequently encountered adverse effects during e-liquid inhalation are irritation of the mouth or throat, dry mouth, a dry cough, nausea, dizziness and headaches[28,41,67,85]. And when e-liquid is projected on the skin or in the eyes, there exist risks of local irritation[41,86]. There have been also been very rare cases of battery explosion[87] or even death after e-liquid ingestion[86,88-90]. Accidental ingestion essentially involved children under 5 years of age. According to different reviews of the literature, e-liquid ingestion is generally far from severe, yielding nothing more serious than nausea, vomiting or hypersalivation[28,86]. In France, the AFNOR norms recommend that child safety devices be affixed to the openings of e-liquid flasks.

Some ingredients are potentially carcinogenic, namely nitrosamines, metallic nanoparticles and formaldehyde. They are present at very low levels in e-liquids and their sprays, in quantities less sizable than those found in tobacco. While their concentrations are generally below the limits defined by health agencies[91], this is not always the case[92].

The short-term effects of nicotine, in a non-smoker or in the event of ingestion, include dizziness, palpitations, nausea, migraine and hypertension[93]. On the other hand, the long-term carcinogenic or teratogenic effects of nicotine have never been conclusively demonstrated[13,93]. While it is true that smoking may have long-term cardiovascular effects, the rare studies in the field suggest the existence of a mechanism through which the smoker develops cardiovascular tolerance of nicotine[86,93-95]. If it is indeed difficult to study a possible casual link between occurrence of cardiovascular diseases and smokers' use of nicotine, this is because concomitantly, they are exposed to the other toxic products contained in tobacco. It should also be noted that no increase in morbi-mortality associated with long-term use of nicotine substitutes has been reported. For more than 30 years, these products have been prescribed to smokers[14,95]. For an even longer period of time, the lethal dose of ingested nicotine in a human being has been estimated at 30 to 60 mg. On 2014, Meyer showed that this estimate was based on the minimally reliable results of self-experiments dating back to … 1856[96]! According to Meyer's new and revised estimates, the median lethal dose in humans would be not 0.8 mg/kg, but rather … 13mg/kg, and the lethal ingested dose would be situated between 500 and 1000 mg of nicotine[96]. Some cases of voluntary e-liquid ingestion have been reported in the

What we know

If the e-cigarette is to effectively contribute to cessation or reduction of tobacco consumption, it must represent an alternative to tobacco smoking that would clearly be less health-damaging. And given its ingredients, e-liquids often cause short-term irritation. There presently exist no morbi-mortality data on the long-term health impact of tobacco cessation thanks to the electronic cigarette, and we are likewise lacking in fully reliable data on the effects of prolonged inhalation of ingested products such as PG, VG and aromas. However, existing toxicological findings suggest that vaping is less harmful than tobacco smoking. That much said, any instrument purportedly facilitating tobacco cessation or reduction needs to be demonstrably effective in a given indication, and up until now, relevant data have been few and far between. Concretely speaking, there has been no methodologically sound clinical trial, and longitudinal studies have presented contradictory results. They nonetheless rather strongly suggest that when e-cigarette use is daily and not associated with concomitant and prolonged tobacco use, it is conducive to attempts at quitting or, at the very least, at cutting down on smoking.

Why is it so difficult in France to arrive at a consensus?

Let's face it: The effectiveness of e-cigarettes will always remain difficult to demonstrate. Most available studies have evaluated the results of first-generation models, even though today's "vapers" privilege second and third-generation models. As a market commodity and under pressure from users, the e-cigarette evolves ever so rapidly, far more rapidly than a pharmaceutical product. Conclusion: Time lags are unavoidable and studies will always be a generation behind in their assessments of the effectiveness or innocuousness of an instrument that will continue to evolve. And, precisely, the singularity of e-cigarette use consists in the possibility for the instrument and its functioning to evolve and be increasingly personalized. Over the course of a single day, vapers have been known to employ e-liquids with differing flavors and nicotine content[112,113]. When disposing of customizable models, they modulate the "vapor" density or the heating temperature of the e-liquid. They may have changed models or concomitantly be using two distinct models in view of diversifying the expected effects[112-115]. Quite clearly, extreme and evolving personalization of e-cigarette use whets vapers' interest in their ongoing pursuit; their ever-changing appropriation and ownership of the tool is difficult if not impossible to capture in studies, particularly in randomized controlled clinical trials.

In France, most health authorities have been applying a precautionary approach to e-cigarettes. In 2015, the *Haute Autorité de Santé* (national authority for health) stated that data were "*still insufficient to recommend it for tobacco weaning*"[117]. In 2016, the *Agence nationale de sécurité du médicament et des produits de santé* (national drug safety agency) positioned the e-cigarette as an "*alternative to classic cigarettes*" but not as medication[34]. In 2016 the *Haut Conseil de la santé publique* (public health council) updated its recommendations, judging that the e-cigarette could be considered as a) an aid to tobacco cessation for smokers wishing to quit and; b) a risk reduction tool[118]. Conclusion: Under present-day conditions it appears difficult for French researchers and caregivers to give simple answers to the complex questions put forward by patients.

As for the continent of Europe, the situation is decidedly heterogeneous. In Switzerland, for example, e-cigarettes are not considered as tobacco-derived products; they are regulated by existing legislation on … foodstuffs. However, sale by professionals of nicotine-containing e-liquids is prohibited, even though the same products can be imported into Switzerland or ordered on Internet sites. In Great Britain, since January 2016 an e-cigarette model (e-Voke) has been considered as a medical device and recognized as an aid to tobacco cessation. It can be prescribed by physicians and reimbursed by the National Health System. To our knowledge, Great Britain is the only European country to have recognized an e-cigarette model as medication. So it is that on the same continent, there coexist 1) a model available on prescription and obtainable over the counter and 2) all the other devices, available only over the counter. The device having received market authorization (MA) as a medication has yet to be commercialized, and the fact that a British cigarette manufacturer has obtained MA renders prevention messages a trifle cacophonous...

Let's stay pragmatic: The fight against tobacco remains primordial

As affirmed by Michael Russell as early as 1991, it behooves physicians to bear in mind that the fight against the use of smoked tobacco is a public health priority of prime importance[119]. Any attempt by a smoker to cut out or even to

cut down on his tobacco use should be strongly encouraged. Some medications are of demonstrated effectiveness as aids to tobacco cessation or diminution, especially when accompanied by information and psychological support, and they should be proposed as first-line treatment. That much said, the objectives and health care strategy have got to stem from a shared medical decision involving both physician and patient. Reduced tobacco use can well be a step on the road to permanent cessation.

When a patient wishes to stop or to reduce smoking by integrating the e-cigarette as an element in his personal initiative and approach, the caregiver should tell the patient that before making a first purchase of an electronic device and e-liquids, he needs to be sure he is fully informed. The physician must detail what is known today about possibly successful tobacco cessation via the e-cigarette, namely the need to personalize use according to the desired effects and the level of addiction; the possibility of modifying use as time goes by; the need to limit "dual use"; and finally, if necessary; the possibility of association with anti-craving treatments.

CONCLUSION

Currently available data in the literature are not sufficiently robust to justify assertions that the e-cigarette is conducive to prolonged tobacco cessation. However, it is known to be far less health-damaging than smoked tobacco; when compared with prolonged tobacco consumption, e-cigarette use may be considered as a means of limiting risks and reducing damage. On an individual scale, the role of the e-cigarette is that which the smoker wishes to assign to it, probably extrinsically to any caregiver advice. That much said, the general practitioner may decide to assume his responsibilities and/or recover his place as a source of support; if he does so, it will be in the framework of shared decision-making. Concretely speaking, he will provide the user with relevant and readily accessible medical information. Having listened to the patient, he will clarify whether or not tobacco addiction exists; if it does, he will apprise himself of its characteristics. He will also clarify the treatment objective, namely control over craving for tobacco, which is the "unreasonable" reason for relapse. Mastery of the urge to smoke is what leads to cessation or reduction of use. In any event, it is as a team that the physicians and the patient choose the instruments conducive to reaching the objective; during this process, the wishes and experience of the patient as well as the latest scientific data will be taken into close account. If the patient wishes to use the e-cigarette without benefiting from medical support, the caregiver should nevertheless advise him to inform himself and test the product in view of facilitating successful adoption. While the health risks entailed by e-cigarette use are much lower than those entailed by inhalation of tobacco combustion products, they are by no means nil. That is why non-smokers should be advised against trying the e-cigarette, and that is also why it need be indicated that this product should always be left out of children's reach. It also matters that the public authorities strengthen their quality controls of e-cigarettes and e-liquids. The most recent AFNOR standards (July 2016) relative to characterization of the emissions respond to these imperatives.

There are some factors, which have only sparsely been explored in studies, that seem to influence the effectiveness of e-cigarettes as instruments facilitating cessation or diminution. These factors include frequency and duration of vaping, e-cigarette model, duration of concomitant tobacco use, presence of nicotine in the e-liquids, and the different aromas and flavors favored. Other factors, which are already known, have been only barely touched upon in studies pertaining to the e-cigarette. They are: initial severity of tobacco addiction, personal feeling of self-efficacy, concomitant utilization of anti-craving medications specifically addressing tobacco addiction. All of these factors should be taken rigorously and systematically into account in studies yet to come. There are few available data on e-cigarettes involving different populations: pregnant women, patients with chronic respiratory or cardiovascular diseases and patients suffering from cancers or psychiatric illnesses. All of these should be the subjects of dedicated studies. And finally, one population seems to be particularly at risk: "vapo-smokers". The risks of prolonged concomitant use of tobacco should be compared to those of smoking alone and to those engendered by prolonged e-cigarette use subsequent to tobacco cessation.

A tutorial on the e-cigarette addressed to health care professionals has been put on line by the Aquitaine AGIR33 association. It is accessible at: http://www.addictutos.com/page/tutoriels

Sidebar 5

Résumé
Bien qu'il existe des médicaments efficaces dans le traitement de l'addiction au tabac, certains fumeurs appréhendent de s'arrêter de fumer ou ne le souhaitent pas. Une démarche de réduction des risques et des dommages pourrait être proposée. La cigarette électronique (ou e-cigarette) est apparue au début des années 2000 comme une façon potentiellement moins dommageable de consommer de la nicotine par voie inhalée. Comme elle n'est pas un médicament en France, la place que les soignants doivent lui donner reste débattue. Les objectifs de cet article étaient de décrire l'usage de l'e-cigarette en France et les connaissances actuelles en matière d'efficacité pour l'arrêt total ou la diminution de la consommation de tabac, et de nocivité. L'usage de l'e-cigarette est surtout un usage des fumeurs/anciens fumeurs et des sujets jeunes. Comme pour le tabac, les niveaux d'usage en France sont parmi les plus élevés d'Europe ; cependant, ils sont stables, voire en baisse depuis 2016. Il n'est pas clairement établi que les e-cigarettes favorisent l'arrêt du tabac. L'usage d'e-cigarettes pourrait cependant favoriser les tentatives d'arrêt ou la réduction des quantités consommées, notamment chez les vapoteurs quotidiens et ceux qui ne s'installent pas dans un usage dualiste prolongé. En l'absence de combustion, l'usage de l'e-cigarette est de loin moins nocif pour la santé que la consommation de tabac fumé.
Conclusion. Toute démarche d'arrêt ou de diminution de l'usage du tabac est à encourager, même avec l'e-cigarette. Dans le cadre d'une décision médicale partagée, le médecin généraliste peut conseiller au fumeur un accompagnement médical et clarifier l'objectif de soin. Il peut proposer les traitements anticraving (patch, varénicline) si le patient accepte la prise en charge de l'addiction ; il utilisera des produits de remplacement en cas de maintien de l'usage du tabac fumé.
➜ Mots-clés : cigarettes électroniques ; arrêt du tabac ; réduction des risques et des dommages.

Summary
Although there are effective medications for the treatment of tobacco addiction, some smokers are afraid to stop smoking or do not want. A harm risk reduction approach can be proposed for such smokers. The electronic cigarette (or e-cigarette) appeared in the early 2000s. It would seem a way less harmful to consume some nicotine by inhalation. In France, it is not considered to be a medical device and its place is unclear to caregivers. Our aims were to describe the e-cigarette use in France, its efficiency (for smoking cessation or reduction) and its harmfulness. E-cigarette use is common among tobacco smokers or former smokers and young subjects. Frequencies of use in France are among the highest in Europe but they remained stable or seemed declining since 2016. It is not yet established that e-cigarettes promote smoking cessation. However, e-cigarette use may encourage attempts to quit smoking or reduce tobacco smoking, in particular among daily users and those who do not settle in a continuous dual use. In the absence of combustion, e -cigarette is far less harmful to health than smoked tobacco.
Conclusion. Any attempt to quit or reduce smoking should be encouraged, even with e-cigarette. In a shared medical decision process, GPs can help smokers by offering medical support and clarifying objectives. Access to treatment of the addiction (patch, varenicline) should be favored; for those who continue tobacco smoking, the use of reinforced nicotine replacement therapy should be facilitated.
➜ Keywords: electronic cigarettes; smoking cessation; harm reduction.

Références

1.World Health Organization. WHO global report. Mortality attributable to tobacco. Geneva : WHO, 2012.
2.Ribassin-Majed L, Hill C. Trends in tobacco-attributable mortality in France. Eur J Public Health 2015;25:824-8.
3.Pasquereau A, Gautier A, Andler R, et al. Tabac et e-cigarette en France : niveaux d'usage d'après les premiers résultats du Baromètre santé 2016. Bull Epidemiol Hebd 2017;12:214-22.
4.American Psychiatric Association. Trouble de l'usage du tabac. In: American Psychiatric Association, Eds. DSM-5 Manuel diagnostique et statistique des troubles mentaux. Issy-les-Moulineaux : Elsevier Masson, 2013.
5.Reynaud M, Benyamina A, Karila L, Aubin HJ. Traité d'addictologie. Paris : Lavoisier, 2016.
6.Binder P. Intervenir sur les addictions en médecine générale. exercer 2017; 129:24-31.
7.Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. Addiction 2004;99:29-38.
8.Hartmann-Boyce J, Stead LF, Cahill K, Lancaster T. Efficacy of interventions to combat tobacco addiction: Cochrane update of 2013 reviews. Addiction 2014;109:1414-25.
9.Auriacombe M. Les substituts font-ils vraiment partie de la thérapeutique ? Rev Mal Respir 2006;23 (Suppl 1):S124-5.
10. Thomas KH, Martin RM, Knipe DW, Higgins JPT, Gunnell D. Risk of neuro- psychiatric adverse events associated with varenicline: systematic review and meta-analysis. BMJ 2015;350:h1109.
11. Vaillant-Roussell H, Cadwallader JS, Gelly J. Sécurité et efficacité des traitements dans le sevrage tabagique. exercer 2017;136:383-4.
12. Stead LF, Koilpillai P, Fanshawe TR, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev 2016;3:CD008286.
13. Russell MA. Realistic goals for smoking and health. A case for safer smoking. Lancet 1974;1:254-8.
14. Houezec JL. La réduction des risques et des dommages est-elle efficace et quelles sont ses limites en matière de tabac ? L'utilisation de nicotine sans combustion. Alcoologie et Addictologie 2017;39:138-47.
15. Scherer G, Lee PN. Smoking behaviour and compensation: a review of the literature with meta-analysis. Regul Toxicol Pharmacol 2014;70:615-28.
16. Auriacombe M. Conseil pour un fumeur et son entourage non fumeur. Le Courrier des Addictions 2011;13:16.
17. Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D. « Cut down to quit » with nicotine

replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis. Health Technol Assess 2008;12:iiiiv,ixxi,1-135.
18. Asfar T, Ebbert JO, Klesges RC, Relyea GE. Do smoking reduction interventions promote cessation in smokers not ready to quit? Addict Behav 2011;36:764-8.
19. Moore D, Aveyard P, Connock M, Wang D, Fry-Smith A, Barton P. Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. BMJ 2009;338:b1024.
20. Shiffman S, Hughes JR, Ferguson SG, Pillitteri JL, Gitchell JG, Burton SL. Smokers' interest in using nicotine replacement to aid smoking reduction. Nicotine Tob Res 2007;9:1177-82.
21. Hughes JR, Carpenter MJ. Does smoking reduction increase future cessation and decrease disease risk? A qualitative review. Nicotine Tob Res 2006; 8:739-49.
22. Hill C. Épidémiologie du tabagisme. Rev Prat 2012;62:325-9.
23. Tverdal A, Bjartveit K. Health consequences of reduced daily cigarette con- sumption. Tob Control 2006;15:472-80.
24. Gerber Y, Myers V, Goldbourt U. Smoking reduction at midlife and lifetime mortality risk in men: a prospective cohort study. Am J Epidemiol 2012;175:1006-12.
25. Hart C, Gruer L, Bauld L. Does smoking reduction in midlife reduce mortality risk? Results of 2 long-term prospective cohort studies of men and women in Scotland. Am J Epidemiol 2013;178:770-9.
26. Pisinger C, Godtfredsen NS. Is there a health benefit of reduced tobacco consumption? A systematic review. Nicotine Tob Res 2007;9:631-46.
27. Office français de prévention du tabagisme. Rapport et avis d'experts sur l'e-cigarette. Paris : OFDT, 2013.
28. Hajek P, Etter J-F, Benowitz N, Eissenberg T, McRobbie H. Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit: Electronic cigarettes: a review. Addiction 2014; 109:1801-10.
29. Etter JF, Bullen C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. Addiction 2011;106:2017-28.
30. Ayers JW, Althouse BM, Allem J-P, Leas EC, Dredze M, Williams RS. Revisiting the rise of electronic nicotine delivery systems using search query surveillance. Am J Prev Med 2016;50:e173-81.
31. Correa JB, Ariel I, Menzie NS, Brandon TH. Documenting the emergence of electronic nicotine delivery systems as a disruptive technology in nicotine and tobacco science. Addict Behav 2017;65:179-84.
32. Glasser AM, Collins L, Pearson JL, et al. Overview of electronic nicotine delivery systems: a systematic review. Am J Prev Med 2017;52:e33-66.
33. European Commission, Directorate-General for Communication. Attitudes of Europeans towards tobacco and electronic cigarettes. Brussels : EC, 2017. Disponible sur : http://ec.europa.eu/commfrontoffice/publicopinion/index. cfm/Survey/getSurveyDetail/instruments/SPECIAL/surveyKy/2146 [consulté le 21 novembre 2017].
34. Agence nationale de sécurité du médicament et des produits de santé. Informations réglementaires relatives à la cigarette électronique - Point d'Information. Paris : Ansm, 2016. Disponible sur : http://ansm.sante.fr/S-informer/ Points-d-information-Points-d-information/ Informations-reglementaires- relatives-a-la-cigarette-electronique-Point-d-Information [consulté le 21 novembre 2017].
35. Directive 2014/40/UE du Parlement européen et du Conseil du 3 avril 2014 relative au rapprochement des dispositions législatives, réglementaires et administratives des États membres en matière de fabrication, de présentation et de vente des produits du tabac et des produits connexes, et abrogeant la directive 2001/37/CE
36. République française. Loi n° 2014-344 du 17 mars 2014 relative à la consom- mation.
37. République française. Loi n° 2016-41 du 26 janvier 2016 de modernisation de notre système de santé.
38. République française. Ordonnance n° 2016-623 du 19 mai 2016 portant transposition de la directive 2014/40/UE sur la fabrication, la présentation et la vente des produits du tabac et des produits connexes.
39. République française. Décret n° 2017-633 du 25 avril 2017 relatif aux conditions d'application de l'interdiction de vapoter dans certains lieux à usage collectif.
40. Pokhrel P, Fagan P, Little MA, Kawamoto CT, Herzog TA. Smokers Who try e-cigarettes to quit smoking: findings from a multiethnic study in Hawaii. Am J Public Health 2013;103:e57-62.
41. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19 000 consumers. Int J Environ Res Public Health 2014;11:4356-73.
42. Christensen T, Welsh E, Faseru B. Profile of e-cigarette use and its relationship with cigarette quit attempts and abstinence in Kansas adults. Prev Med 2014;69C:90-4.
43. Hummel K, Hoving C, Nagelhout GE, et al. Prevalence and reasons for use of electronic cigarettes among smokers: Findings from the International Tobacco Control (ITC) Netherlands Survey. Int J Drug Policy 2015;26:601-8.
44. Ooms GI, Bosdriesz JR, Portrait FRM, Kunst AE. Sociodemographic differences in the use of electronic nicotine delivery systems in the European Union. Nicotine Tob Res 2016;18:724-9.
45. Farsalinos KE, Poulas K, Voudris V, Le Houezec J. Electronic cigarette use in the European Union: analysis of a representative sample of 27 460 Europeans from 28 countries. Addiction 2016;111:2032-40.
46. Wang M, Wang JW, Cao SS, Wang HQ, Hu RY. Cigarette smoking and electronic cigarettes use: a meta-analysis. Int J Environ Res Public Health 2016; 13. pii: E120.
47. Rutten LJ, Blake KD, Agunwamba AA, et al. Use of e-cigarettes among current smokers: associations among reasons for use, quit intentions, and current tobacco use. Nicotine Tob Res 2015;17:1228-34.
48. Ramo DE, Young-Wolff KC, Prochaska JJ. Prevalence and correlates of electronic-cigarette use in young adults: findings from three studies over five years. Addict Behav 2015;41:142-7.
49. Pasquereau A, Guignard R, Andler R, Nguyen-Thanh V. Electronic cigarettes, quit attempts and smoking cessation: a 6-month follow-up. Addiction 2017;112:1620-8.
50. Coleman BN, Johnson SE, Tessman GK, et al. « It's not smoke. It's not tar. It's not 4000 chemicals. Case closed »: exploring attitudes, beliefs, and perceived social norms of e-cigarette use among adult users. Drug Alcohol Depend 2016;159:80-5.
51. Sherratt FC, Newson L, Marcus MW, Field JK, Robinson J. Perceptions towards electronic cigarettes for smoking cessation among Stop Smoking Service users. Br J Health Psychol 2016;21:421-33.
52. Rooke C, Cunningham-Burley S, Amos A. Smokers' and ex-smokers' understanding of electronic cigarettes: a qualitative study. Tob Control 2016;25:e60-6.

53. Barbeau AM, Burda J, Siegel M. Perceived efficacy of e-cigarettes versus nicotine replacement therapy among successful e-cigarette users: a qualitative approach. Addict Sci Clin Pract 2013;8:5.
54. Simmons VN, Quinn GP, Harrell PT, et al. E-cigarette use in adults: a qualitative study of users' perceptions and future use intentions. Addict Res Theory 2016;24:313-21.
55. Fontaine A, Laugier S, Artigas F. Étude qualitative auprès des utilisateurs de cigarette électronique (pratiques, usages, représentations). Paris : LRSH, 2016. Disponible sur : http://www.lrsh.fr/wp-content/uploads/2016/ 04/LRSH-E-Cigarette-RAPPORT-FINAL-vDEF-17-6-2016.pdf [consulté le 20 novembre 2017].
56. Caponnetto P, Campagna D, Cibella F, et al. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-Month randomized control design study. PLoS One 2013;8:e66317.
57. Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. Lancet 2013;382:1629-37.
58. Pearson JL, Stanton CA, Cha S, Niaura RS, Luta G, Graham AL. E-cigarettes and smoking cessation: insights and cautions from a secondary analysis of data from a study of online treatment-seeking smokers. Nicotine Tob Res 2015;17:1219-27.
59. Vickerman KA, Carpenter KM, Altman T, Nash CM, Zbikowski SM. Use of electronic cigarettes among state tobacco cessation quitline callers. Nicotine Tob Res 2013;15:1787-91.
60. Manzoli L, Flacco ME, Ferrante M, et al. Cohort study of electronic cigarette use: effectiveness and safety at 24 months. Tob Control 2017;26:284-92.
61. Biener L, Hargraves JL. A longitudinal study of electronic cigarette use among a population-based sample of adult smokers: association with smoking cessation and motivation to quit. Nicotine Tob Res 2015;17:127-33.
62. Manzoli L, Flacco ME, Fiore M, et al. Electronic cigarettes efficacy and safety at 12 Months: cohort study. PLoS One 2015;10:e0129443.
63. Hitchman SC, Brose LS, Brown J, Robson D, McNeill A. Associations between e-cigarette type, frequency of use, and quitting smoking: findings from a longitudinal online panel survey in Great Britain. Nicotine Tob Res 2015;17:1187-94.
64. Zhu SH, Zhuang YL, Wong S, Cummins SE, Tedeschi GJ. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. BMJ 2017;358:j3262.
65. Brose LS, Hitchman SC, Brown J, West R, McNeill A. Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up. Addiction 2015;110:1160-8.
66. Grana RA, Popova L, Ling PM. A longitudinal analysis of electronic cigarette use and smoking cessation. JAMA Intern Med 2014;174:812-3.
67. Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev 2016; 9:CD010216.
68. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. Lancet Respir Med 2016;4:116-28.
69. Malas M, Tempel J van der, Schwartz R, et al. Electronic cigarettes for smoking cessation: a systematic review. Nicotine Tob Res 2016;18:1926-36.
70. Dawkins L, Turner J, Crowe E. Nicotine derived from the electronic cigarette improves time-based prospective memory in abstinent smokers. Psychopharmacology 2013;227:377-84.
71. Lechner WV, Meier E, Wiener JL, et al. The comparative efficacy of first- versus second-generation electronic cigarettes in reducing symptoms of nicotine withdrawal. Addiction 2015;110:862-7.
72. Bahl V, Lin S, Xu N, Davis B, Wang Y, Talbot P. Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. Reprod Toxicol 2012;34:529-37.
73. Romagna G, Allifranchini E, Bocchietto E, Todeschi S, Esposito M, Farsalinos KE. Cytotoxicity evaluation of electronic cigarette vapor extract on cultured mammalian fibroblasts (ClearStream-LIFE): comparison with tobacco cigarette smoke extract. Inhal Toxicol 2013;25:354-61.
74. Behar RZ, Davis B, Wang Y, Bahl V, Lin S, Talbot P. Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. Toxicol In Vitro 2014;28:198-208.
75. Yu V, Rahimy M, Korrapati A, et al. Electronic cigarettes induce DNA strand breaks and cell death independently of nicotine in cell lines. Oral Oncol 2016;52:58-65.
76. Wu Q, Jiang D, Minor M, Chu HW. Electronic cigarette liquid increases inflammation and virus infection in primary human airway epithelial cells. PloS One 2014;9:e108342.
77. Husari A, Shihadeh A, Talih S, Hashem Y, El Sabban M, Zaatari G. Acute xxposure to electronic and combustible cigarette Aerosols: effects in an animal model and in human alveolar cells. Nicotine Tob Res 2016;18:6139.
78. Williams M, Villarreal A, Bozhilov K, Lin S, Talbot P. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. PloS One 2013;8:e57987.
79. Allen JG, Flanigan SS, LeBlanc M, et al. Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a sample of 51 products, including Fruit-, Candy-, and Cocktail-Flavored e-cigarettes. Environ Health Perspect 2016;124:733-9.
80. Centers for Disease Control and Prevention (CDC). Fixed obstructive lung disease among workers in the flavor-manufacturing industry--California, 2004-2007. Morb Mortal Wkly Rep 2007;56:389-93.
81. McAuley TR, Hopke PK, Zhao J, Babaian S. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. Inhal Toxicol 2012;24:850-7.
82. Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tob Control 2014;23: 133-9.
83. Goniewicz ML, Gawron M, Smith DM, Peng M, Jacob P, Benowitz NL. Exposure to nicotine and selected toxicants in cigarette smokers who switched to electronic cigarettes: a longitudinal within-subjects observational study. Nicotine Tob Res 2017;19:160-7.
84. Hecht SS, Carmella SG, Kotandeniya D, et al. Evaluation of toxicant and carcinogen metabolites in the urine of e-cigarette users versus cigarette smokers. Nicotine Tob Res 2015;17:704-9.
85. Chen IL. FDA summary of adverse events on electronic cigarettes. Nicotine Tob Res 2013;15:615-6.
86. Farsalinos KE, Polosa R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. Ther Adv Drug Saf 2014;5:67-86.
87. Walsh K, Sheikh Z, Johal K, Khwaja N. Rare case of accidental fire and burns caused by e-cigarette batteries.

BMJ Case Rep 2016;2016.
88. Chen BC, Bright SB, Trivedi AR, Valento M. Death following intentional ingestion of e-liquid. Clin Toxicol 2015;53:914-6.
89. Ordonez JE, Kleinschmidt KC, Forrester MB. Electronic cigarette exposures reported to Texas poison centers. Nicotine Tob Res 2015;17:20911.
90. Gupta S, Gandhi A, Manikonda R. Accidental nicotine liquid ingestion: emerging paediatric problem. Arch Dis Child 2014;99:1149.
91. Varlet V, Farsalinos K, Augsburger M, Thomas A, Etter J-F. Toxicity Assessment of Refill Liquids for Electronic Cigarettes. Int J Environ Res Public Health 2015;12:4796-815.
92. Chen J, Bullen C, Dirks K. A Comparative Health Risk Assessment of Electronic Cigarettes and Conventional Cigarettes. Int J Environ Res Public Health 2017;14.
93. Institut national de recherche et de sécurité pour la prévention des accidents du travail et des maladies professionnelles. Nicotine. Fiche toxicologique n°312. Paris : INRS, 2016.
94. Benowitz NL, Jacob P, Herrera B. Nicotine intake and dose response when smoking reduced-nicotine content cigarettes. Clin Pharmacol Ther 2006;80:703-14.
95. Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. Trends Cardiovasc Med 2016;26:515-23.
96. Mayer B. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. Arch Toxicol 2014;88:5-7.
97. Schipper EM, de Graaff LCG, Koch BCP, et al. A new challenge: suicide attempt using nicotine fillings for electronic cigarettes. Br J Clin Pharmacol 2014;78:1469-71.
98. Cho JH, Paik SY. Association between Electronic Cigarette Use and Asthma among High School Students in South Korea. PloS One 2016; 11:e0151022.
99. McConnell R, Barrington-Trimis JL, Wang K, et al. Electronic cigarette use and respiratory symptoms in adolescents. Am J Respir Crit Care Med 2017;195:1043-9.
100. Polosa R, Morjaria JB, Caponnetto P, et al. Persisting long term benefits of smoking abstinence and reduction in asthmatic smokers who have switched to electronic cigarettes. Discov Med 2016;21:99-108.
101. Bertholon JF, Becquemin MH, Roy M, et al. Comparison of the aerosol produced by electronic cigarettes with conventional cigarettes and the shisha. Rev Mal Respir 2013;30:752-7.
102. Bunnell RE, Agaku IT, Arrazola RA, et al. Intentions to smoke cigarettes among never-smoking US middle and high school electronic cigarette users: National Youth Tobacco Survey, 2011–2013. Nicotine Tob Res 2015; 17:228-35.
103. Moore GF, Littlecott HJ, Moore L, Ahmed N, Holliday J. E-cigarette use and intentions to smoke among 10-11-year-old never-smokers in Wales. Tob Control 2016;25:147-52.
104. Primack BA, Soneji S, Stoolmiller M, Fine MJ, Sargent JD. Progression to traditional cigarette smoking after electronic cigarette use among US adolescents and young adults. JAMA Pediatr 2015;169:1018-23.
105. Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. JAMA 2015;314:700-7.
106. Barrington-Trimis JL, Urman R, Berhane K, et al. E-cigarettes and future cigarette use. Pediatrics 2016;138:e20160379.
107. Spindle TR, Hiler MM, Cooke ME, Eissenberg T, Kendler KS, Dick DM. Electronic cigarette use and uptake of cigarette smoking: a longitudinal examination of U.S. college students. Addict Behav 2017;67:66-72.
108. Gautier S, Kinouani S, Raherison C. Do electronic cigarettes increase the risk of smoking among adolescents and young adults? Sante Publique 2017;29:333-40.
109. Wills TA, Sargent JD, Gibbons FX, Pagano I, Schweitzer R. E-cigarette use is differentially related to smoking onset among lower risk adolescents. Tob Control 2016;26:534-9.
110. Etter JF. Gateway effects and electronic cigarettes. Addiction 2017.
111. Almalki M, Gray K, Sanchez FM. The use of self-quantification systems for personal health information: big data management activities and prospects. Health Inf Sci Syst 2015;3:S1.
112. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Spyrou A, Voudris V. Impact of flavour variability on electronic cigarette use experience: an internet survey. Int J Environ Res Public Health 2013;10:7272-82.
113. Cooper M, Harrell MB, Perry CL. A qualitative approach to understanding real-world electronic cigarette use: implications for measurement and regulation. Prev Chronic Dis 2016;13:E07.
114. Yingst JM, Veldheer S, Hrabovsky S, Nichols TT, Wilson SJ, Foulds J. Factors associated with electronic cigarette users' device preferences and transition from first generation to advanced generation devices. Nicotine Tob Res 2015;17:1242-6.
115. Etter JF. Characteristics of users and usage of different types of electronic cigarettes: findings from an online survey. Addiction 2016;111:72433.
116. Etter JF. Throat hit in users of the electronic cigarette: an exploratory study. Psychol Addict Behav 2016;30:93-100.
117. Haute Autorité de santé. Avis n° 2015.0100/AC/SBPP du 4 novembre 2015 du collège de la Haute Autorité de santé sur la nécessité d'actualiser la recommandation de bonne pratique : « Arrêt de la consommation de tabac : du dépistage individuel au maintien de l'abstinence en premier recours » (octobre 2014), suite au rapport sur la cigarette électronique du Public Health England. 2015. Saint-Denis : HAS, 2015.
118. Haut Conseil de la santé publique. Avis relatif aux bénéfices-risques de la cigarette électronique ou e-cigarette étendus en population générale. Rev Mal Respir 2016;33:509-25.
119. Russell MA. The future of nicotine replacement. Br J Addict 1991;86:653-8.