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REVIEW

Electronic Nicotine Delivery Systems (ENDS): Implications for the Clinician

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ABSTRACT

The evidence that tobacco cigarettes are harmful to the health of smokers led to the introduction of electronic nicotine delivery systems (ENDS) as a safer alternative. ENDS, which include electronic cigarettes (e-cigs) and heated tobacco products (battery-operated devices that heat a liquid and produce an aerosol), are portable, cheap, easy-to-use, self-powered devices, and resemble tobacco cigarettes. After an overview of the toxicological, clinical, and epidemiological implications associated with the increasingly widespread use of ENDS, this narrative paper evaluates their role as a smoking cessation aid. Randomized controlled trials show that e-cigs can help in achieving cigarette smoking cessation, but their role in real life is still debated. There is no clear association in current smokers between the prevalence of e-cig use and overall quit rates. Although ENDS are not Food and Drug Administration (FDA)- and European Medicines Agency (EMA)-approved for quitting, they are one of the most widely utilized pharmacological support devices for smoking cessation. Physicians should ask for ENDS use and amount at each visit, be able to advise on how to manage ENDS as an aid for quitting, encourage vapers not to continue their use indefinitely, and explain how to stop ENDS.

Keywords: Harm reduction; Nicotine; HTP; Tobacco; Cigarette; Electronic cigarette; Smoking; ENDS; Vaping

Key Summary Points

The diffusion of electronic nicotine delivery systems (ENDS) worldwide raises new possibilities and doubts about their impact on people's health.

This article offers an overview of the opportunity to favor smoking cessation through ENDS use compared to traditional nicotine replacement therapy (NRT).

The utility of ENDS must be weighed against the still unknown possible long-term adverse effects of these new devices on patients' health.

The topic is still highly debated, as can be seen from the differences in opinions between the main scientific associations regarding this issue.

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INTRODUCTION

Electronic nicotine delivery systems (ENDS) include electronic cigarettes (hereinafter referred to as e-cigs) and heated tobacco products (hereinafter referred to as HTPs). A brief history of ENDS is shown in Fig. 1. Many extensive reviews for details of ENDS composition and mechanisms of action [1–5] can be found in the literature. These devices are portable, cheap, and self (battery)-powered, have a discreet and convenient design resembling tobacco cigarettes, and produce aerosols containing nicotine without any combustion. The "modern" e-cigs have better performance and easier use and maintenance than previous models, and novel generations of devices are continuously marketed. There are a range of different e-cigs that differ in shape, flavor, use, maintenance, and performance. Among the proposed classifications of e-cigs, we suggest distinguishing between disposable and rechargeable/refillable e-cigs, where either the tank is periodically replaced with ready-to-use e-liquid or the e-liquid is manually refilled with the possibility of customizing it (Table 1 and Figs. 1, 2). We will only deal with e-cigs containing nicotine; they contain an e-liquid with different nicotine concentrations. Only e-liquids with nicotine concentrations ≤ 20 mg/mL (2%) are available in the European Union (EU) [6], whereas in other countries, such as the United States, there are no restrictions on nicotine concentration. In addition to nicotine, the e-liquid usually contains water, glycerol, propylene glycol, and flavorings. HTPs are devices containing tobacco sticks. The stick is a paste containing tobacco, flavors, cellulose, guar gum, and propylene glycol. The best-selling HTP is IQOS (I Quit Ordinary Smoking) by Philip Morris International, but other products are very common. The widespread use of ENDS has several implications for clinicians. After a toxicological, clinical, and epidemiological overview, this narrative paper focuses on the role of the clinician dealing with daily ENDS users.

WHY IS IT IMPORTANT, BUT DIFFICULT, TO STOP CIGARETTE SMOKING? HOW CAN SMOKING CESSATION RATE INCREASE?

Cigarette smoking is a leading preventable cause of death, disease, and disability. Quitting at any age is associated with lower excess mortality. People who quit at ages 35–44, 45–54, and 55–64 gain approximately 9, 6, and 4 years relative to continuing to smoke, respectively [7]. Due to the evidence that cigarette smoking is harmful, many smokers want to stop smoking, but they do not always succeed in quitting. Less than 5–10% of smokers who try quitting alone

Table 1 The most commonly used e-cigs by type

Most popular e-cigarettes brands	
Rechargeable	**Disposable**
KIWI	Vuse
Juul	Elfbar
Vaporesso	Dinner Lady
JustFog	GeekBar
Joyetech	Blubar
Eleaf	Lost Mary

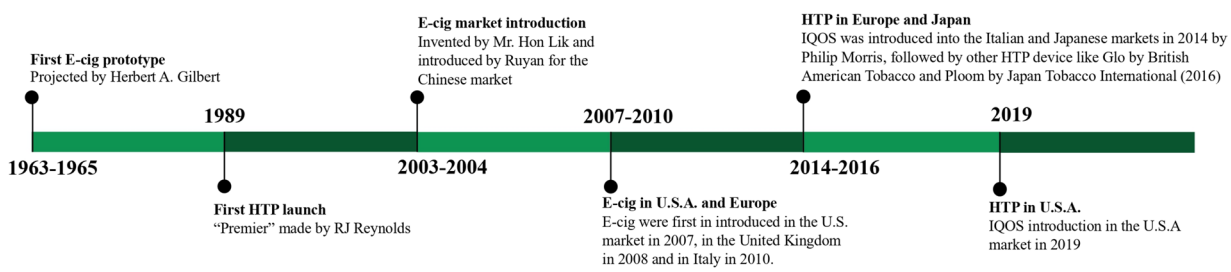

Fig. 1 Timeline of electronic nicotine delivery systems (ENDS) history

Fig. 2 Main differences between e-cig devices

achieve sustained smoking abstinence at 1 year of follow-up [8]. Smoking cessation assistance increases quitting rates, but it is seldom available, and therefore most smokers try quitting alone. An analysis of smoking cessation attempts in the EU found that almost three-quarters of smokers in 2017 (74.8%) had tried to quit alone [9]. Long-standing evidence shows that some pharmacological therapies properly provided to smokers motivated to quit are effective and safe for quitting and, in combination with behavioral support, achieve sustained abstinence rates of 30% at 1-year follow-up. Currently approved pharmacotherapies to support smokers in quitting include nicotine replacement therapy (NRT), such as nicotine patches, gum, and inhalers, the α4β2 nicotinic acetylcholine receptor partial agonists varenicline and cytisine, and the dopamine and noradrenaline reuptake inhibitor bupropion, alone or in combination [10]. The uptake of nicotine, the main psychoactive component of tobacco, from cigarette smoking is the main cause of difficulties in quitting. Nicotine stimulates the nicotinic acetylcholine receptors of the body, primarily in the central and peripheral nervous system. Notably, not only is the substance a key determinant for most positive psychotropic effects of nicotine, but the speed of absorption is a key factor as well. Smoke from cigars or pipes has an alkaline pH (about > 6.5) and permits a moderate and relatively slow absorption of nicotine through the mucosal mouth. Smoke from tobacco cigarettes produces an acidic environment (i.e., pH 5.5–6.0), permitting a faster and larger absorption of nicotine through the lungs, with peaks in plasma and brain within a few tens of seconds after inhalation, as shown in Figs. 3 and 4. After inhalation, nicotine is rapidly metabolized, prompting the smoker to inhale again to obtain further positive psychotropic effects. In addition, the continuous use of nicotine by tobacco cigarette smokers desensitizes the receptors, leading to the development of tolerance and dependence. By regular smoking throughout the day, the dependent cigarette smoker guarantees stable concentrations of nicotine in the brain, and any voluntary or involuntary cessation of smoking provokes withdrawal symptoms, such as agitation, anxiety, insomnia, difficulty concentrating, tiredness, irritability, and increased appetite [11]. The need for cigarette smoking is not only physical, but also psychological. This is closely related to the gestures, cues, and routine act of smoking. Every action in the day becomes associated with the gratification of nicotine intake through a mechanism that, in addition to the peak of nicotine at the brain level, evokes an element linked to a reassuring, primordial regressive symbolism tied to the hand-to-mouth ritual.

Recently marketed e-cigs contain nicotine salt formulations that have a smoother taste in the mouth and are less irritating than their free-base variety, improving the sensory experience of vaping and optimizing nicotine absorption, with pharmacokinetics resembling that of tobacco cigarettes. Similar findings are observed with recent HTPs [12–16]. Of course, the bioavailability of nicotine depends not only on the device, but also on the technique and the experience of the user. Comparative studies show similar degrees of nicotine dependence between users of some novel ENDS and traditional cigarettes [17–19]. We have displayed the kinetics of blood nicotine after smoking tobacco cigarettes, e-cigs, and HTPs, and the use of some NRT in Fig. 4. NRT products, when properly used, ensure relatively constant levels of nicotine in the blood

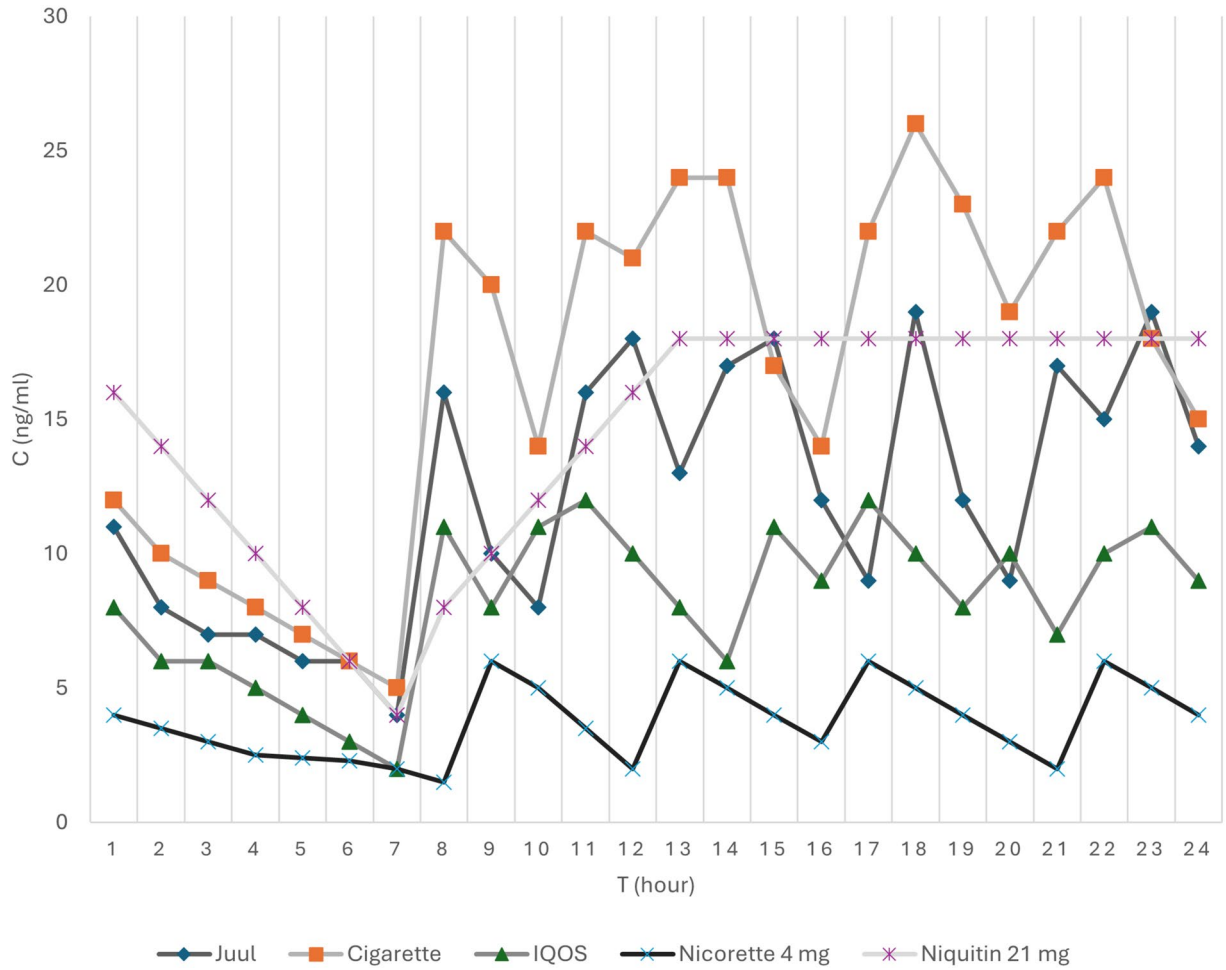

Fig. 3 Pharmacokinetic comparison of nicotine plasma levels over a 24-h period between tobacco cigarettes, some electronic nicotine delivery systems (ENDS), and nicotine replacement therapy (NRT) [104–107]. It can be seen how the nicotine plasma levels rise and fall during a normal day of a daily user of e-cigs, HTPs (heated tobacco products), cigarettes, or NRT. Every spike corresponds to smoking a cigarette, an IQOS (HTP), or a JUUL (e-cig), or using an NRT (patches like Nicorette/Niquitin). The graph shows how NRT has a constant and regular standard level which can be controlled depending on the dose of the NRT. On the other end, cigarettes have the highest spike of dose, followed by e-cigs, and lastly by HTPs

and brain over 24 h, controlling withdrawal symptoms, but do not sustain rewarding effects associated with nicotine peaks obtainable by smoking tobacco cigarettes.

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Clinical Consequences of Inhalation from ENDS

Combustion, absent with the use of ENDS [17], is responsible for most of the toxic substances inhaled with cigarette smoking. Many studies (mostly those sponsored by manufacturers of

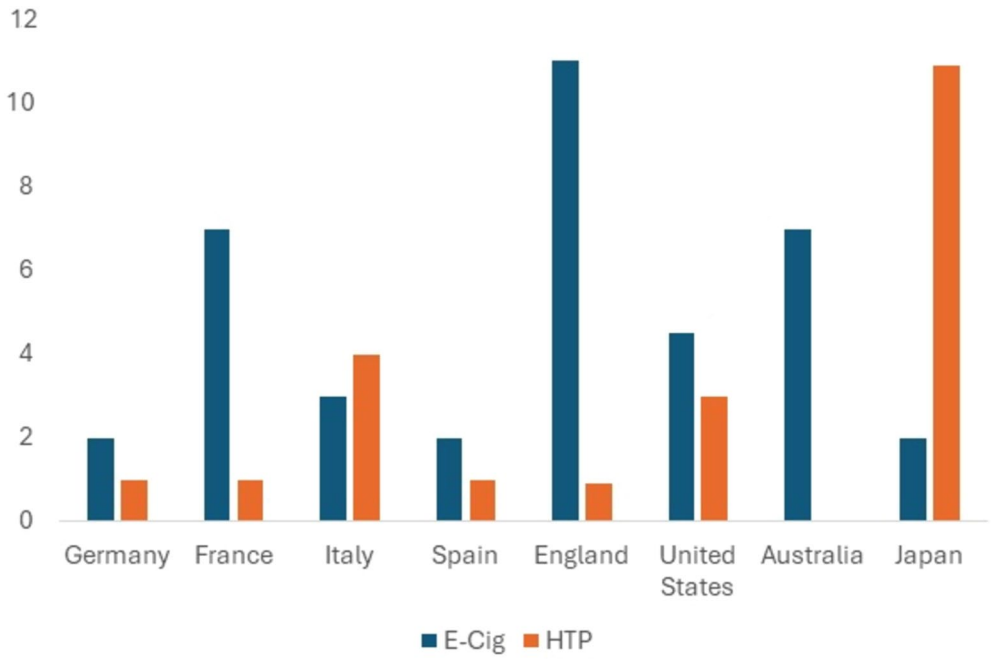

Fig. 4 Current daily users of e-cigs and heated tobacco products (HTPs) worldwide [103, 108–113]

ENDS) show that the concentration of traditional toxicants inhaled with ENDS is lower—often much lower—than the concentration that results from inhaling cigarettes [20]. However, the health risks are not linearly related to exposure to inhaled toxicants. In addition, other toxicants, such as valeraldehyde, acrolein, and acenaphthene, are found in aerosols from ENDS at similar or even higher concentrations than those observed when smoking tobacco cigarettes [1–5, 21–23]. There are many case reports of acute lung damage associated with the use of e-cigs [24]. E-cig- or vaping-associated lung injury (EVALI), the epidemic occurring in the USA, mostly in young people, with serious and even fatal acute lung damage associated with vaping, has caused great concern [25]. Although most cases have been attributed to unorthodox vaping of tetrahydrocannabinol with vitamin E acetate [25], EVALI confirms the harmful risks inherent to possible manipulation of e-liquids, common among young people [26]. Moreover, the use of e-cigs may increase the frequency of exacerbations or wheezing and worsen respiratory function in individuals with asthma and chronic obstructive pulmonary disease (COPD) [24, 27–29]. On the other hand, other studies reported that the switch from cigarette smokers to e-cigs only may reduce the frequency of exacerbations and attenuate respiratory symptoms compared to those who continued to smoke [30].

Less information is available on the health risks related to the use of HTPs. The Japan Society and New Tobacco Internet Survey (JASTIS) cross-sectional study found adverse respiratory effects in HTP users; in addition, among patients with cancer scheduled for surgery, the occurrence of airway obstruction in current exclusive HTP users was greater than in never-tobacco users [31]. Another small study comparing 19 COPD patients switching to HTPs versus a matched control group who continued to smoke did not find any significant difference in COPD Assessment Test (CAT) score, exercise capacity, or exacerbation rate at 3-year follow-up [32]. The use of ENDS has been associated with oxidative stress and endothelial damage, and nicotine itself has a known stimulant effect on heart rate and blood pressure. However, the cardiovascular effects of ENDS might be of less clinical relevance than tobacco cigarettes [33]. In

a nationwide Korean study, switching to e-cigs in patients following percutaneous coronary intervention was associated with a lower rate of major adverse cardiovascular events than continuing smoking [34]. Another nationwide Korean study found that, compared with cigarette-only smokers, individuals who quit tobacco cigarettes and switched to ENDS only use had a lower risk for subsequent cardiovascular disease (adjusted hazard ratio [aHR] 0.81, 95% confidence interval [CI], 0.78–0.84). However, recent cigarette quitters with ENDS use had a higher risk for cardiovascular events than recent cigarette quitters without ENDS use (aHR 1.31; 95% CI 1.01–1.70). In addition, compared with long-term cigarette quitters without ENDS use, long-term quitters with ENDS use had higher cardiovascular risk (aHR 1.70; 95% CI 1.07–2.72 [35]).

A last key question is related to the risk of health harms for proxies of ENDS users. Cases of worsening of asthma and/or other lung diseases have been reported in individuals passively exposed to e-cigs [24, 36, 37]. Switching from smoking to vaping indoors may substantially reduce, but not eliminate, second-hand exposure to nicotine and other noxious substances [38]. There is less dispersion of toxicants from the mainstream and a shorter half-life of the particulate exhaled by ENDS users than that emitted by cigarette smokers [39].

Epidemiological use of ENDS

The diffusion of ENDS is now worldwide, albeit with differences between geographical areas (see Figs. 4, 5), related to both commercial factors (different promotion of manufacturers) and local laws. HTPs are mostly popular in Japan, where the sale of nicotine e-cigs is heavily restricted [40]. HTP use remains occasional in the UK and Northern Europe. The use of e-cigs prevails in the UK, where around 9% of the adult population use them, with just over half using them daily [41]. In the cross-sectional Smoking Toolkit Study [42], 85% of individuals who reported using e-cigs in their attempt to stop smoking cigarettes and quitting successfully became long-term vapers. However, in recent years in England, an increase in long-term vaping has been observed not only in former smokers, but

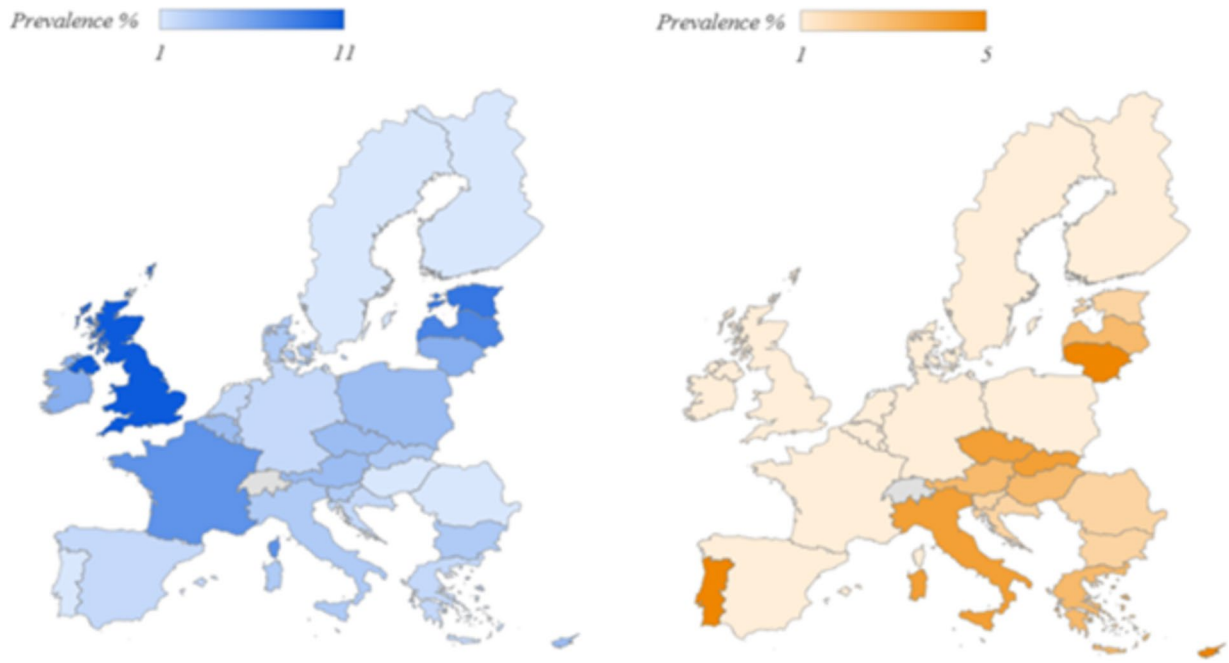

Fig. 5 Current daily users of e-cigs and HTPs worldwide [103, 108–113]

even in individuals who continued to smoke tobacco cigarettes (dual smokers) [41]. Some studies have shown that simultaneous use of cigarettes and ENDS could have worse health consequences than the use of tobacco cigarettes only [24, 43]. The fate of former cigarette smokers who started ENDS afterwards is unclear. One study shows that at 1-year follow-up, many long-term vapers relapse to cigarette smoking (44%) [44]. From 2021 in England, the rate of vapers also increased considerably in never-smokers, mainly driven by young adults [45] using disposable e-cigs (50%). Many authors think that e-cig use may act as a gateway to subsequent traditional cigarette smoking. The Global Youth Tobacco Survey recently found rates of dual smokers up to 10% of Italian and Latvian 13–15-year-olds [46]. The use of novel e-cigs with the potential to induce dependence is particularly worrying in never-smoker adolescents, for whom disposable e-cigs are banned in the UK beginning in summer 2025. In 2018, 90.5% of HTP users in Canada, the USA, England, and Australia were dual smokers [47]. E-cig users are also increasing (>50% in most countries of the study from the Global Youth Tobacco Survey) and seem to be more prone to starting after conventional cigarette smoking than never-users, becoming "dual smokers" [48]. Some studies found that HTP use in former smokers was associated with a higher risk of relapse than no-HTP use [49, 50].

Role of ENDS as a Smoking Cessation Aid

Manufacturers have proposed ENDS as cigarette smoking cessation aids. Unlike in the UK, where e-cigs have been endorsed by the Royal College of Physicians as an acceptable smoking cessation aid [51], ENDS are not approved by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) to aid motivated smokers in quitting. Based on randomized controlled trials (RCTs), a Cochrane analysis showed that the use of e-cigs increased rates of smoking cessation versus no pharmacological treatment (odds ratio [OR] 2.37, 95% CI 1.73–3.24; 16 RCTs, 3828 participants [52]). A few large studies have compared different pharmacological treatments as help for smoking cessation. An RCT study in 458 individuals motivated to quit found biochemically confirmed abstinence at 26 weeks in 61 of 152 participants (40.4%) in the e-cig group versus 67 of 153 (43.8%) in the varenicline group and 30 of 153 (19.7%) in the placebo group ($P<0.001$); no serious adverse events were reported [53]. Another study suggested that the combination of varenicline and e-cigs increased quitting rates versus the varenicline-only arm [54]. A large RCT including 886 participants found a 1-year abstinence rate of 18% in the e-cig group versus 10% in the NRT arm (relative risk [RR] 1.83; 95% CI 1.30–2.58; $P<0.001$). At the end of the study, many e-cig users who quit continued to vape (80% vs. 9% for the NRT arm, [55]). A Cochrane review showed a clear advantage for quitting in individuals using e-cigs (OR 2.37, 95% CI 1.73–3.24), varenicline (OR 2.33, 95% CI 2.02–2.68), cytisine (OR 2.21, 95% CI 1.66–2.97), or a combination of NRT (OR 1.93, 95% CI 1.61–2.34) and, to a lesser degree, nicotine patch (OR 1.37, 95% CI 1.20–1.56), other NRT alone (OR 1.41, 95% CI 1.29–1.55), and bupropion (OR 1.43, 95% CI 1.26–1.62). There is evidence that e-cigs increase quit rates compared to a single NRT (RR 1.59, 95% CI 1.30–1.93; seven studies, 2544 participants) and moderate-certainty evidence that they increase quit rates compared to e-cigs without nicotine (RR 1.46, 95% CI 1.09–1.96; six studies, 1613 participants) [10].

The ultimate role of e-cigs as a smoking cessation aid in real life remains debated. Some studies showed an advantage for e-cigs [52, 56], while others did not [57–59], either in adult smokers in general (OR 0.95; 95% CI 0.77–1.16) or in the subgroup motivated to quit (OR 0.85; 95% CI 0.68–1.06). It is possible that differences in the methods and populations between studies were too great to draw firm conclusions. Current cigarette smokers usually start using ENDS as a smoking cessation aid, but also to guarantee nicotine intake (and avoid withdrawal symptoms) in settings where cigarette smoking is forbidden, or simply enjoy being dual users. It is also unclear whether ENDS use can bolster motivation to quit cigarette smoking. A recent

naturalistic RCT [60] evaluated the effect of offering free e-cigs to smokers not motivated to stop smoking cigarettes. At a 6-month follow-up, quitting was observed in 17% of participants in the active arm (9% switchers and 8% complete quitters) versus 9% of the control group (6% complete quitters and 3% switchers). In longitudinal cohort studies, daily but not non-daily e-cig use was associated with higher odds of prolonged cigarette smoking abstinence compared to no e-cig use [57, 61, 62]. Some studies showed that e-cigs with higher nicotine content led to more days of smoking abstinence than lower concentrations [12, 63]. An RCT study [64] reported a relatively unsuccessful result (quit rate 7.3% at 6 months) using an e-cig with very low nicotine content (3 mg/ml). By contrast, e-cig devices and flavors are not considered to be associated with cigarette discontinuation rates [65–67]. Less information is available on the role of HTPs as a smoking cessation aid. A Cochrane analysis including 13 relevant studies (11 trials supported by tobacco companies) up to January 2021 [68] compared unwanted effects and toxin levels in individuals randomly assigned to use HTPs, to continue smoking cigarettes, or to abstain from tobacco use. Unfavorable symptoms in the short-term studies (average 13 weeks) were uncommon. An RCT including 211 individuals not motivated to quit compared the effects of the IQOS 2.4 Plus versus a refillable e-cig for 12 weeks. The abstinence rate did not differ significantly between arms at the end of the study (39.1% vs. 30.8%); therefore, the authors concluded that further studies will be needed to confirm their findings [69].

Cessation Help in ENDS Used Seeking Support for Cessation

It is increasingly reported that e-cig users may not be able to quit alone and may need help to quit. In a sample of 1988 US e-cig users, of whom 1053 and 540 were dual users and former cigarette smokers, respectively, 302 participants (15%) claimed having made a past-year quit attempt, and 1208 participants (61%) reported plans to quit e-cigs [70]. Vapers who perceived themselves as being addicted were less likely to achieve abstinence [71]. Therefore, effective interventions are needed to help individuals quit e-cigs. At present, vaping cessation help is based on the translation of results from smoking cessation studies [72]. No medication is currently approved by the FDA or EMA for vaping cessation. The UK Medicines and Healthcare products Regulatory Agency has approved a nicotine-containing mouth spray, already licensed for smoking cessation, for vaping cessation [73]. Varenicline demonstrated efficacy in a study including 140 daily e-cig users motivated to quit vaping. Participants were randomized to receive either varenicline (1 mg, administered twice daily for 12 weeks) plus counseling or placebo plus counseling for 12 weeks, followed by another 12-week follow-up, non-treatment phase. The biochemically validated continuous abstinence rate was significantly higher for varenicline than placebo at 12-week follow-up (40.0% vs. 20.0%; OR 2.67, 95% CI 1.25–5.68, $P<0.02$) and at 24 weeks (34.3% vs. 17.2%; OR 2.52, 95% CI 1.14–5.58, $P<0.05$ [74]). An exploratory trial including 30 adult daily e-cig users (50% were dual smokers) also suggested acceptable efficacy (33%, all e-cig-only users) for NRT (21-mg patches, 4-mg lozenges) plus behavioral support with 7-day point abstinence [75]. Another randomized study conducted in a remote area found that in young people (18–24 years old) regularly using e-cigs and motivated to quit, the offer of NRT increased the quit rate at the 3-month follow-up by seven points—a good albeit nonsignificant increase [76]. A double-blind RCT in 131 US adults who only vaped daily and wanted to quit found greater continuous e-cig abstinence in the active arm using a 12-week treatment with cytisine 3 mg three times daily versus the placebo group at week 16 (23.4% vs. 13.2%; OR 2.00; 95% CI 0.82–5.32; $P=0.15$ [77]).

The issue of ENDS has started to attract the attention of scientific societies. Their positions on the use of these devices as a tool for smoking cessation vary and are summarized in Table 2. The lack of clear positions can be explained by the dichotomy between the experience of ENDS

Table 2 Scientific societies' positions about the use of e-cigs as smoking cessation support [114–124]

	Pro	Against	Interlocutory
American Heart Association (AHA)		■	
Australian Government-Australian College of General Practitioners	■		
CDC			■
European Association of Preventive Cardiology			■
European Respiratory Society (ERS)		■	
European Commission (EC)		■	
NICE-NHS	■		
New Zealand Government	■		
United States Preventive Servicessent Task Force (USPSTF)			■
WHO		■	

used as a smoking cessation tool and the possible effects that these devices could have in the long term. Further studies, particularly on the long-term effects of ENDS on human health, are needed.

CONCLUSIONS

Although promoted as cigarette smoking cessation aids, manufacturers first proposed ENDS

as consumer products, probably for commercial reasons. While RCTs show that e-cigs—the most commonly used type of ENDS—may be effective as smoking cessation aids, their role in real life is debated. At present, there is no clear association between the prevalence of e-cig use among current smokers and overall quit rates [78]. Some scientific organizations endorse the use of ENDS to help in quitting and believe that they can reduce exposure to harmful chemicals with respect to tobacco cigarette smoking, at least if the cigarette user is able to switch completely away from smoking [79–81]. Other associations advise against the use of ENDS (Table 2 [82–96]), as their effect on health in the long term is unknown, but not risk-free. In addition, the recent increased use of novel e-cigs mainly in never-smoker youth is a matter of concern, because exposure to nicotine during adolescence can damage normal brain development [97, 98], seems to increase the potential for abuse liability [99], and is associated with increased risk of subsequent smoking initiation with respect to never-vapers [48, 100]. Health authorities strictly monitor ENDS use, usually consider them to be tobacco products, and try to place limitations on their wide commercialization, above all in never-smoker adolescents. However, it should be remembered that strict restrictions might lead people to seek other ways to find ENDS, as shown by the large role of the black market in Australia, where selling e-cigs without a medical prescription was forbidden [101].

Regardless of our own opinion on ENDS and the health risks described in the previous sections, physicians should regularly ask for ENDS use at each visit (see Table 4 for main suggested items, i.e., recording how much and which ENDS are used [type—disposable, not disposable; use at least once a day, not daily], and the nicotine dosage). In a large sample of 134,931 US adult patients referred to primary care clinics in 2022, rates of e-cig screening ($n = 46{,}997$; 34.8%) were significantly lower than those for tobacco (99.5%) and alcohol (96.2%) use [102]. Clinicians should also know how to manage ENDS. They should discourage uptake of ENDS among never-smokers and long-term former smokers, advise against dual smoking, and suggest ENDS use only for quitting cigarettes. ENDS is now the most widely used pharmacological support for smoking cessation not only in the UK (where e-cigs have been promoted as support for quitting), but even in the USA, France (27% of attempts), Greece (26%), Germany (15%), and Italy (7%, 103). Many experts do not suggest ENDS as the first-choice pharmacological treatment in individuals requiring support for cigarette cessation attempts, but we cannot exclude their use if the individual desires it, eventually in association with other drugs. Dependent dual smokers who succeed in stopping cigarettes should gradually reduce their vaping frequency or nicotine strength only when they feel confident that they can do this without going back to smoking. E-cigs should not be used indefinitely. Proper information from health caregivers might play a critical role in success among smokers using ENDS for quitting [125]. In this respect, it may be interesting to remember the findings of a national US cohort study where smokers who used e-cigs on their own were less successful in quitting [58].

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Declarations

Conflict of Interest. Jean-Guillaume Starnini, Federico Nigroli, Giulio Natalello, Elena Bargagli, and Andrea Sisto Melani have nothing to disclose.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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