Electronic cigarettes for smoking cessation: an opportunity to readdress smoking cessation treatment

To the Editor:

E-cigarettes have been licensed as a quitting tool in order to decrease the devastating effects of tobacco smoking. In the European Respiratory Society task force report published last year, we stated that, at the present time, the evidence for licensed smoking cessation medications was stronger compared to e-cigarettes [1]. 1 year later, a pragmatic randomised controlled trial comparing nicotine replacement therapy (NRT) and e-cigarette effectiveness in smoking cessation was published by the *New England Journal of Medicine*, with results favouring e-cigarettes (18%) compared to NRT (9,9%) [2]. This was the third randomised controlled trial performed, after the ASCEND and ECLAT [3] trials, comparing e-cigarette and NRT efficacy in smoking cessation. The purpose of this correspondence is to analyse these randomised controlled trials as studies comparing two different nicotine delivery systems (e-cigarettes and NRTs) from three perspectives: addiction, smoking cessation and safety.

With regards to addiction, we already know that the pharmacokinetic properties of nicotine and the way it is processed by the body contribute to its addictiveness (figure 1) [10]. When nicotine enters the lungs through the inhalation route (electronic, combusted and heated cigarettes), it is absorbed rapidly from pulmonary arterial circulation and delivered quickly in high concentrations to the brain, so that nicotine levels peak within 7–10 s of inhalation (figure 1) [10]. However, the acute effects of nicotine dissipate quickly, along with the associated feelings of reward; this rapid cycle causes the smoker to continue dosing to maintain nicotine's pleasurable effects and prevent withdrawal symptoms, leading to both satisfaction and addiction (figure 1). In contrast, NRTs deliver nicotine through systemic circulation that results in decreased and slowly delivered concentrations of nicotine in the blood (figure 1), which are less addictive and do not lead to satisfaction [10]. Additionally, vapers are more likely to have a COPD diagnosis, indicating high addiction levels [11]. Moreover, the dosage of nicotine taken while on e-cigarettes cannot be assumed, as nicotine intake differs per e-cigarette brand and inhalation manoeuvres [10].

In terms of effectiveness, and contrary to established 1-year monotherapy abstinence rates (20–23%) [8, 9, 12, 13] for NRT patches combined with intense behavioural support [14] and for NRTs combination (20.2–36.5%; patches and gums or lozenges) [8, 9, 12, 13], the study by Hajek *et al.* [2] shows rates of 9.9%, which surprisingly are even less than those of placebo (13.8%) in reiterated pharmaceutical treatment trials [8, 9, 12, 13]. Similarly, lower abstinence rates were seen for NRTs both in the ASCEND (5.8%) and ECLAT (9%) trials [3].This deviation, compared to hundreds of NRT trials [8, 9, 12, 13], explains the basic principles of nicotine addiction and treatment.

Namely, NRTs are very effective as first line treatment for the disease [15] of nicotine addiction only when subject to proper prescription, tailoring and use, meaning not being under-dosed both in dosage and duration [8, 9, 12, 13]. Precisely, NRTs should be tailored according to the intensity of smoking and used at least for 3 months that somatic addiction persists [8–13], as suggested from guidelines. Undoubtedly, effectiveness is further enhanced when combined with behavioural support [10, 14] from trained healthcare professionals in order to address the psychological compound of nicotine addiction.

Furthermore, it is known that prior success or failure with smoking cessation medication is often a major determinant of medication choice [16] and therefore whether the smoker has used treatments in the past,

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The effectiveness of e-cigarettes for smoking cessation still lacks a valid endorsement. It is timely to treat the chronic disease of nicotine addiction safely and effectively, by incorporating smoking cessation guidelines to our everyday practice. https://bit.ly/3gUjGRM

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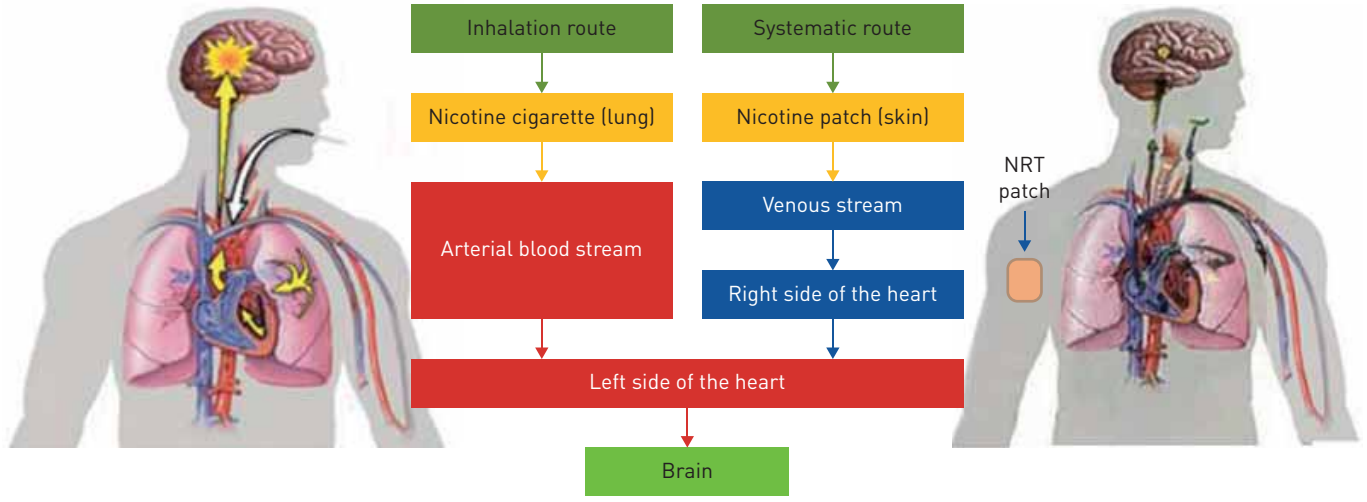

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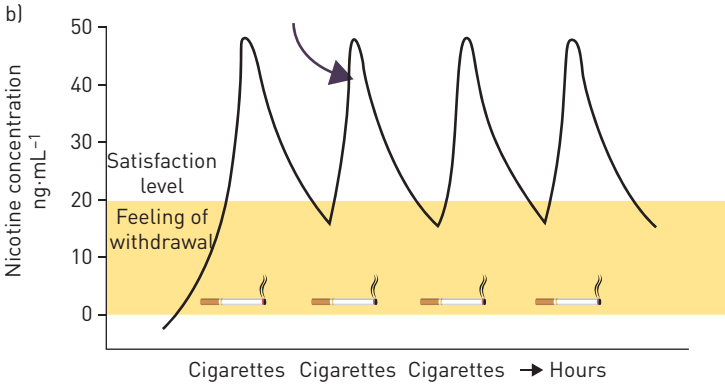

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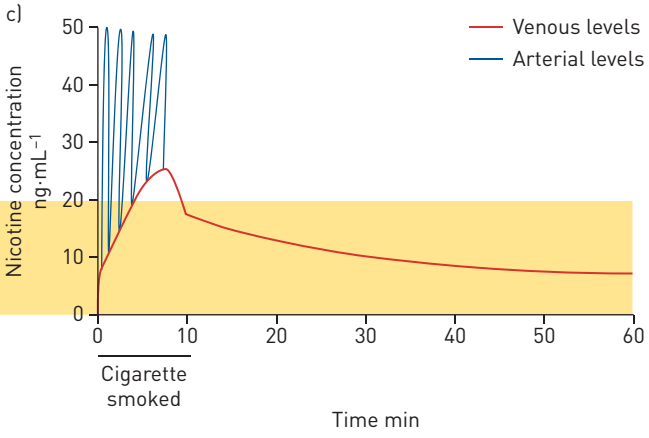

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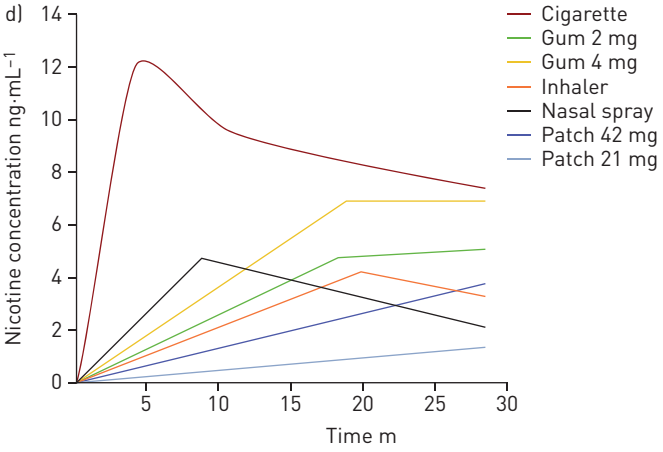

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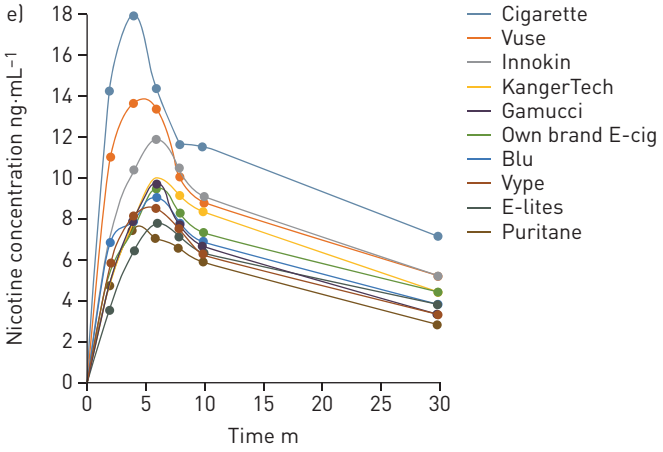

f)

Medication	Estimated OR	Estimated abstinence rate %
Placebo	1.0	13.8
Varenicline	3.1	33.2
Nicotine patch	1.9	20.8–23.4
Nicotine gum	1.5	19.0
Bupropion SR	2.0	24.2
Patch and gum (ad lib)	3.6	20.2–36.5
Patch and bupropion	2.5	28.9

FIGURE 1 a) Arterial and venous levels of nicotine through inhalation and systemic route. When tobacco smoke reaches the small airways and alveoli of the lung, nicotine is rapidly absorbed. After a puff, high levels of nicotine reach the brain in 7–20 s, faster than with intravenous administration. Adapted from [4, 5]. b, c) Blood concentrations of nicotine rise quickly during a smoke and peak at the completion of smoking [4, 5]. d) Schematic illustration of nicotine concentrations obtained from single dose administration of NRTs and smoking. Smoking produces much higher nicotine levels and much more rapidly than all forms of NRTs. Reproduced from [6] with permission from the publisher. e) Nicotine delivered from e-cigarettes through the inhalation route in a manner that is very similar to that of combusted tobacco. Reproduced from [7] with permission. f) Effectiveness of first line smoking cessation treatment. Adapted from [8, 9].

compliance with the treatments, their perceived efficacy and their adverse events, and the smoker's current treatment preferences, should be discussed. In the study reported by Hajek *et al.* [2], there was no provision to mitigate all these effects, except from treatment preference. Furthermore, since in the context of smoking cessation clinics, NRT has a track record of effectiveness from 19 to 36% (figure 1) [9, 12, 14], it gives an impression that abstinence rates of 10% are seen in usual practice in England [2]; maybe reflecting NHS decrease in funding and the hardening hypothesis of smokers, although this is less probable. Additionally, over half of quit attempts in England are made with the help of e-cigarettes, demonstrating the willingness of smokers to use these products as cessation aids in large numbers in countries which promote their use [17], to the detriment of NRTs [18]. Since in the trials reported by Hajek *et al.* [2], the majority of smokers in both arms had failed in previous quitting attempts using NRTs, their previous negative experience in combination with an environment that promotes e-cigarettes could result in characterisation of NRTs as an inferior option from participants of the NRTs group, who could have put less effort into their quit attempt than those in the e-cigarette group. In support of this, adherence to treatment from participants in the NRT arm was lower (7.4%) than in the e-cigarette arm (41%). In contrast, in the e-cigarette arm, a free choice of e-liquid was permitted, while flavoured e-liquids have been proved to be more attractive to users, e-cigarettes were cheaper and 80% of smokers continued vaping for 12 months.

Finally, regarding safety, NRTs are given over the counter because of their extremely safe profile with almost no contraindications [8, 9, 12, 13]. Their safety has additionally been proved in high doses and prolonged time. The opposite could be argued for e-cigarettes in long-term usage.

Lack of experience and financial resources for smoking cessation may lead clinicians to shortcuts such as e-cigarettes. However, recent acute hazards revealed for e-cigarettes [19] and public health concerns [20] (renormalising smoking, undermining smokers' wish to quit and ex-smokers' wish to stay smoke-free, dual use, initiating smoking in minors) make this call for incorporating smoking cessation guidelines in our clinical practice timely.

NRT use for tobacco harm reduction is evidence-based [21], extremely safe and less addictive than e-cigarettes. We acknowledge that e-cigarettes may provide health benefits compared to continued smoking for smokers that have previously made quit attempts. However, since addiction is maintained and may lead to switching or dual usage [20], their long-term effects [1] are unknown and they provide weaker evidence compared to licensed smoking cessation medications, we urge for exhaustion of optimal behavioural and pharmaceutical treatment for smoking cessation.

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