Cue Reactivity to Electronic Cigarettes: A Systematic Review

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ABSTRACT: Cue reactivity to Electronic Nicotine Delivery Systems (ENDS) has been studied by several researchers, yet the variability in user types (smokers, former smokers, dual users, exclusive ENDS users) and ENDS designs used between the studies may have undermined consistent results. This systematic review aims to give an overview of ENDS cue reactivity and how smoking status and device design may moderate this. A systematic search of Medline, Embase, Web of Science, PubMed and Cochrane was completed. All studies which reported findings on reactivity to ENDS cues in the form of craving or desire for ENDS or cigarettes, attention to cue, delay of gratification or economic decisions were included. Exclusion criteria were non-human subjects, non-adult participants or participants with comorbidities. Literature selection was carried out by 2 independent reviewers. The risk of bias and study quality were assessed using tools developed by Cochrane, BMJ and NHLBI. A total of 711 papers were screened and 22 studies were included in the current review. Study design, research question(s), population of interest, number of participants, dependent variable(s), ENDS generation and nicotine content used and study results were extracted. ENDS cues reliably induced ENDS craving, with no clear moderation by smoking status and no apparent moderation by device generation. In about half of the studies, ENDS cues induced craving for conventional cigarettes. Most studies used a smoker sample, thus limiting the conclusions that can be drawn on the moderation of cue reactivity by smoking status. The quality varied among studies but comparing the findings against the outcomes of only high-quality studies did not yield any different results. The results of this review support the notion of cue reactivity to ENDS, identifies gaps in current research on different user types and implies that ENDS design iterations have little impact on cue reactivity.

KEYWORDS: Cue reactivity, electronic cigarettes, electronic nicotine delivery systems, smoking, craving, systematic review

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Introduction

The electronic cigarette is a handheld electronic device that was introduced in the early 2000’s as a replacement or substitute for conventional cigarettes¹,² and has become increasingly popular over the last two decades.³,⁴ More formally, it goes by the name of Electronic Nicotine Delivery System (ENDS) or Electronic Non-Nicotine Delivery System (ENNDS); although the distinction may be confusing as the delivery of nicotine depends on the nicotine content of the e-liquid rather than the device used. As newer devices allow the user to refill with different e-liquids, an ENNDS may become an ENDS and vice versa depending on which e-liquid is used as a refill. To avoid confusion, this paper will use the term ENDS to refer to the device, regardless of the nicotine content of the e-liquid.

Since their introduction, ENDS have gone through several design iterations and the modern devices look quite different from the original cigarette-like designs.⁵,⁶ Parallel to this transformation, the ENDS user profile has diversified into different types such as active conventional tobacco smokers attempting to quit or trying to reduce tobacco consumption (dual users), former conventional cigarette smokers who only vape and ENDS users only, who never smoke tobacco cigarettes⁵,⁷ Due to the nicotine in the solution that is inhaled, ENDS users are susceptible to dependency,⁸ yet little is known about how this dependency takes shape in the face of the variety of devices and user profiles. The current systematic literature review aims to give an overview of existing studies on reactivity to ENDS-related cues and the potential moderating role of device design and user status.

ENDS

In principle, the mechanism of all ENDS devices consists of a battery-powered heating element (the ‘atomiser’) which heats the e-liquid, a solution usually consisting of propylene glycol or glycerol (glycerine), nicotine and flavouring agents. The resulting nicotine-containing aerosol (also called vapour) is returned to the user to be inhaled.¹,⁵,⁶ Initially, ENDS were promoted and marketed as a healthier alternative to tobacco cigarettes as well as to assist with quitting tobacco smoking.¹,² Although the effectiveness of vaping for smoking cessation remains unclear,⁹,¹⁰ the World Health Organisation has recommended that ENDS should not been marketed for this purpose¹¹ as
First generation ENDS (‘cig-a-likes’ or ‘vape-sticks’), started to be commercialised in the mid 2000’s. These devices have a fixed low-voltage battery and are designed to mimic the cigarette experience. Initially, the devices consisted of three separate pieces (atomising unit, e-liquid reservoir, battery), evolving into a two-piece (combining the atomising unit and reservoir) and disposable single-piece.

Second-generation ENDS (clearomisers or tank systems) have a larger battery. They are often pen-shaped, comparatively larger and can contain more e-liquid than the first generation ENDS. Clearomisers are transparent and the atomiser unit is removable.

Third-generation ENDS are known as ‘mods’. They allow the user to modify the battery qualities (voltage, wattage, power and even charging other devices) making them easier to adjust and have been marketed as ‘vapes’.

The fourth generation of ENDS is known as ‘pods’, and is sometimes merged with the third generation of mods. It was introduced in 2015 (e.g., JUUL). These devices have fixed batteries (meaning less control over the settings) which are generally more powerful than the first- and second-generation ENDS. They are suitable for use with nicotine salts rather than freebase nicotine, allowing users to inhale higher nicotine doses with a decreased taste aversion. Pods are very variable in design, smaller and sleeker than previous ENDS generations and are highly popular.

Along with the evolution of design and marketing, the ENDS user profile has also changed, from current smokers using ENDS as an alternative to conventional cigarettes (dual users), former smokers who only use ENDS and exclusive ENDS users who have never smoked. The latter tend to be younger and are more likely to use flavoured e-liquid, especially fruit, mint, menthol and candy/dessert flavours. This trend of young and non-smoking users has raised concerns regarding potential health risks associated to ENDS use, particularly linked to harmful substances contained in flavoured vape products, as well as due to nicotine being highly addictive and how it can be detrimental to adolescent brain development (which continues until users are in their mid 20s), and the association of nicotine with disturbances of cognitive development in teens and young adults. In addition, concerns have been raised about the potential risk of young people who vape to be susceptible to smoke tobacco cigarettes in the future.

ENDS and cue reactivity

Given the first generation’s cig-a-like design and appeal to cigarette smokers, it may not be too surprising that ENDS use was initially considered a variation of conventional cigarette use. With the progression into more modern devices as the newer generations were developed and their appeal to a much wider array of users, it has become clear that ENDS are their own brand of stimulant. Currently, there is no universally accepted framework of behaviours which constitute typical ENDS usage, or at what level of usage someone should be considered either dependent or a regular user.

Cue reactivity is often seen as a fundamental part of addiction, being considered a relevant risk factor in substance-related behaviours and it may, therefore, be the best starting point for establishing the addictive qualities of a product. The Pavlovian conditioning, or classical conditioning, states that when an individual is exposed to two paired stimuli, these can elicit responses. Cues are neutral stimuli that, through repeated pairings, may become conditioned to a substance or drug leading to cue reactivity. This cue reactivity can happen when an individual interacts with environmental contexts or a stimulus, such as food advertisements, the smell of cigarettes or the sight of alcohol. Conditioned stimuli can cause different natural responses (conditioned or learned responses) such as physiological (eg, salivation, sweating), behavioural (eg, drug seeking and consumption), psychological (eg, anxiety, irritability) and a symbolic expression or a subjective motivational state (craving) in response to external cues.

The term ‘craving’ has been the focus of many interpretations and often is defined as a synonym of urge or desire. For example, for the American Psychological Association (APA), craving refers to an insistent desire, urge or yearning, which is commonly used as a criteria for drugs related diagnoses. For some, there are distinctions between craving and urge, whereby the former can be defined as a motivational state similar to the subjective desire for the effects of a drug and the latter indicates a behavioural intention to engage in a particular behaviour. Regardless of the lack of consensus for a prevalent definition, craving and urge have been largely associated with cue exposure and cue-reactivity.

Furthermore, substance cues can have an effect on the level of self-reported craving and self-administration behaviours. The individual’s risk of relapse may be predicted by the degree of cue reactivity.

The classical conditional concept has been used to support several theories related to alcohol and other drugs (AOD) craving, such as that developed by Winkler, which indicates that addicts going through craving could be motivated to look for AODs in order to be relieved of conditioned withdrawal effects. This model was first used to explain heroin addiction and has
been applied to alcohol among other drugs. Cue reactivity has long been established in conventional smoking\textsuperscript{52-54} as well as for the study and treatment of other disorders such as eating related disorders,\textsuperscript{46} gaming,\textsuperscript{45} alcoholism\textsuperscript{56} and drug use.\textsuperscript{57}

However, whether cue reactivity prevails over the range of user profiles and ENDS generations is still under investigation. On one hand, one could argue that ENDS cues are similar enough to smoking cues for smokers to respond with craving when exposed to them: ENDS and cigarettes use roughly the same hand-to-mouth gestures; assuming that e-liquid with nicotine content is used, both deliver their nicotine through inhalation; and most (but not all) ENDS create clouds of vapour similar in appearance to cigarette smoke. On the other hand, ENDS designs can differ wildly from both cigarettes and one another. This could mean that, for example, a user of the cig-a-like will not respond with craving at all when exposed to a pod, because the latter looks so different from the device that they have been conditioned on that it does not elicit a response, particularly if it does not produce vapour clouds. Similarly, a smoker may respond only to first-generation ENDS cues with craving, as the later generations are too dissimilar.

**Objectives of the current review**

The current systematic literature review aims to create an overview of ENDS cue reactivity, as well as investigate the moderating role that the device’s generation and smoking status of the user (i.e., dual users – who use both ENDS and tobacco cigarettes, former smokers who only vape and users who have never smoked and only use ENDS) may play in ENDS cue reactivity. The research questions are as follows:

- Do ENDS cues elicit cravings for conventional (tobacco) cigarettes, ENDS or both?
- Is this response moderated by user smoking status?
- Is this response moderated by ENDS generation or design?

The review is limited to studies using adult participants with no relevant comorbidities (e.g., other addictions, cancer, psychological disorders). The intervention of interest is cue reactivity (be it visual, olfactory, social or other cues), with the primary outcome of interest being cue-induced craving, and the following possible secondary outcomes: delay of gratification, attention to cue, time to next ENDS or cigarette use, and money users are willing to spend to use an ENDS or cigarette. Comparisons of interest would be ENDS cue reactivity to alternative cue reactivity (e.g., tobacco smoking cue, neutral cue or comparing different generations of ENDS devices) and comparing ENDS cue reactivity depending on smoking status: dual user, former smoker who only vapes, or ENDS user who only vapes. To give a complete overview of the state of the field, experimental study designs, cross-sectional, cohort studies, case studies, randomised controlled trials, pre-post tests without a control group, longitudinal studies, as well as literature reviews were included.

**Method**

**Protocol**

A PROSPERO protocol was adapted from an earlier logged protocol (CRD42020153927), which was deemed too comprehensive. However, at the time of writing the updated protocol was still under review. The protocol can also be found at the Open Science Framework under the digital object identifier 10.17605/OSF.IO/XK9NA.

**Eligibility criteria, information sources and search**

The PRISMA guidelines for review\textsuperscript{58,59} were followed for the current review. Five databases (Ovid Search-MEDLINE, Ovid search-EMBASE, Web Of Science, Pub Med and Cochrane) were searched by a single researcher using the following search terms: [‘vaping’ OR ‘e-cigarette’ OR ‘electronic cigarette’ OR ‘electronic nicotine delivery’] AND [‘cognitive control’ OR ‘cue reactivity’ OR ‘cue exposure’ OR ‘cue induc*’ OR ‘vaping cue’ OR ‘reactivity to cue’ OR ‘e-cigarette cue’ OR ‘salien*’ OR ‘stimulus’ OR ‘withdrawal symptoms’] AND NOT [‘animal’ OR ‘mice’ OR ‘cannabis’ OR ‘marijuana’], in the title, keywords or abstract. No language restrictions were considered for the database searches, although all search terms were written in English only. There was no limit of the year of publication for literature searches, since relevant research related to the use of electronic cigarettes is relatively new. The reference lists of selected papers were also scanned for relevant papers.

**Inclusion criteria.** The inclusion criteria were as follows: any study with an adult participant population targeting cue reactivity to ENDS was included. Cue reactivity was taken as a physiological or psychological response to the cue. Measures of primary interest were reports of craving and desire, but brain responses, cognitive measures and behavioural measures were also included.

**Exclusion criteria.** The following excluding criteria were observed: the use of non-human subjects, the inclusion of subjects with comorbidity (psychopathological or physical), the inclusion of non-adult subjects, data that had been published in another paper included in the review (these two or more publications were to be treated as one), papers written in any language other than English, studies on vaping any drug other than nicotine or a placebo aerosol liquid, and studies that compared smoking cigarettes to vaping.

**Study selection**

Paper selection occurred in three stages. First, all duplicates were removed. Then, paper screening occurred based on the title and abstract. Finally, the sample of papers that was left was reviewed based on the full paper contents. During this final stage, paper accretion through identifying relevant publications...
in the literature which were not uncovered by the database search occurred as well. Newfound publications were also assessed for inclusion/exclusion criteria.

Reviewing took place through the Covidence interface, with two reviewers independently screening and selecting all papers to verify inclusion criteria and to confirm relevance. Group discussions were conducted when discrepancies regarding the inclusion of studies occurred.

Data extraction

The following variables were extracted from the selected studies: study design, the population of interest (age group, smoking and vaping background), number of participants, independent variables, dependent variable(s), generation and type of ENDS device used in each study (when reported), nicotine content e-liquid used (if applicable), procedure, research question(s), results, funding and reported conflicts of interest.

As part of the paper evaluation, quality control tools were used. Specifically, the Cochrane Risk of Bias tool (ROB 2.0) was used for assessing the quality of randomised trials, and the Risk of Bias In Non-randomised Studies of Interventions (ROBINS-I) for cohort-type studies. The PRISMA 2009 Checklist was used for assessing systematic reviews and meta-analyses. Finally, the Study Quality Assessment Tools developed by the National Heart, Blood and Lung Institute (NHLBI) were used to assess overall quality.

Table 1 shows a summary of the selected papers, their design, their main findings and the risk of bias.

Results

Study selection

The search was completed in October 2020 and resulted in a total of 1009 papers: Cochrane (n = 59), Ebscohost (n = 182), Embase (n = 131), MEDLINE (n = 67), Pubmed (n = 111), Scopus (n = 577). After duplicate removal, 711 papers remained. Of those, 679 were excluded based on their title or abstract, leaving 32 papers from the original search for the full-text review. During this stage, one more paper was identified through the bibliographic references resulting in a total of 33 papers for full-text review. Of those 33, two were removed for including non-adults among their participants, eight were removed because they did not include cue exposure in their design and one was removed because it was a protocol with no outcomes reported. Thus, the current systematic literature review included a total of 22 papers. See Figure 1 for the flow-chart of the selection process; see Table 1 for the data extracted and assessed risk of bias per study.

Preliminary findings

Over half the papers (n = 12) used a between-subjects randomised design. Three papers had a mixed pre-post test design, where participants completed a baseline measure, were randomly allocated to a condition and completed a post-exposure measure; five had within-participant experimental designs; one study had a pre-post test with no control group; and one carried out a regression analysis.

Overall, the quality of the studies was high, with 14 receiving a ‘good’ grade, five receiving a ‘fair’ grade and three a ‘poor’ on the NHBLI tools. The risk of bias was low overall, with four studies receiving ‘some concerns’ and one being identified as ‘high risk’ (Table 1). In terms of funding and potential conflicts of interest, several authors reported being previously affiliated with the Food and Drug Administration (FDA) or various pharmaceutical companies; none reported affiliation with the tobacco or vaping industry. Similarly, funding was received from a number of sources outside of academic institutions such as the National Cancer Institute (NCI) or National Institute for Drug Abuse (NIDA); none from the tobacco or vaping industry, although one study used vape products (devices and cartridges) provided by the manufacturer, White Super E-cigarette.

Almost all studies (n = 19) used smoking participants (either exclusively smoking or dual users) in their experiments; of those, one compared smokers to former smokers and those who had never smoked, one compared smokers to dual users, those who are exclusively ENDS users and those who are neither smokers nor ENDS users; one compared daily to intermittent ENDS users to former smokers. Of the remaining three papers that did not include smokers, one included participants who had never smoked and did not currently smoke, one assessed only exclusive ENDS users, and one included both current and former smokers but analysed the groups separately. All papers used visual cues.

In addition, 18 studies informed about the type (generation or commercial brand) of ENDS used in their experiments as cues (e.g., in person use or visualisation, in videos, advertisement, or printed ads) (Table 1). Moreover, ENDS were used either as a unique active cue or compared with other ENDS generations or tobacco cigarette cues. In this way, 10 studies used first generation ENDS, five studies used second generation, five studies used third generation and two studies reported the use of fourth generation ENDS. Furthermore, two studies reported the use of participants’ own ENDS (unspecified) and two studies reported the commercial brand but not the ENDS specifications. In regards to nicotine content, only 10 studies reported the ENDS nicotine levels used in their experiments. E-liquids nicotine content ranged from 0 to 59 mg/ml (salt). Further information about ENDS types and nicotine levels used in the reviewed studies, including related outcomes, is presented in the sub-sections below and in Table 1.

Do ENDS elicit cravings for conventional (tobacco) cigarettes ENDS or both?

The main outcome investigated in this narrative systematic review was related to cue reactivity to ENDS. To achieve this, information related to three primary associated cravings...
Table 1. Summary of the selected papers, their design, main findings and risk of bias.

| REF             | POPULATION (N) | STUDY DESIGN | ENDS GENERATION / TYPE (MG/MG/NIQUITINE) AND BRAND | RESEARCH QUESTION(S) | PRIMARY OUTCOME | SECONDARY OUTCOMES | MEASUREMENTS | RESULTS | ROB AND SQ |
|-----------------|----------------|--------------|-----------------------------------------------------|-----------------------|-----------------|--------------------|--------------|---------|------------|
| Lochbuehler et al | Former (N=38), current (N=46), and never (N=48) smokers (N=132 total) | Between subject 2 (cue: first generation ENDS vs third generation ENDS) × 2 (smoking status: smoker/former smoker/never smoker) design, random assigned. | 1, 3 (Cigalike and MOD) (NA) | Do ENDS capture and hold attention, and is this associated with tobacco craving? | Craving for tobacco cigarettes | Attention to cues whether device type (cigalike or mod) moderated associations between attention measures and craving for tobacco cigarettes, intention to use ENDS and attitudes towards using ENDS. Results did not differ by device type; cigalike and mod cues evenly affected viewing. | 16 ENDS pictures (cigalike/mod related scenes and 16 pictures of similar scenes with no ENDS cues, and additional 26 pictures pairs. Cigalike and mod Visual Probe Task-VPT) | Visual attention measure: Eye tracking while completing a visual probe task. Measures: Craving was assessed before and after the task. Attentional bias scores: dwell time and latency of initial fixation. Reaction time. | Smokers looked longer at ENDS related images than former smokers and non-smokers. Smoking status (group) had a main effect on conventional cigarette craving: smokers reported higher craving levels than former smokers did. Smoking status had a main effect on intention to use ENDS than the other 2 groups. Longer dwell time on ENDS cues associated with more favourable attitudes towards ENDS. ENDS cues may contribute to craving for tobacco cigarettes. | L; G |
| Blackwell et al | Regular smokers (N=278), dual users (N=96), regular ENDS users (N=282) and non-users (N=280) (total N=936) | Between subject 4 (cue: first generation ENDS vs third generation ENDS vs cigarette vs control) × 4 (smoking status) design Random assigned to watch video online | 1, 3 (NA) First gen.: cigalike Third gen.: Tank | 1. Are smoking urges following exposure to ENDS cues higher than neutral cues? 2. Do third generation ENDS elicit lower smoking urges than first gen ENDS? | Urge to smoke | Urge to vape, desire to smoke and vape and intention to quit or remain abstinent from smoking. | 4 videos (random): smoking, vaping (cigalike or tank) or neutral. | Online experiment Visual attention to 1 min cue video (according to condition) and related questionnaire. Measures: Questionnaire of smoking or vaping urges. Desire for cigarette/ENDS. Likelihood to quit smoking or remain abstinent. | No effect of cue on urge or desire to smoke or smoke and vape; urge for ENDS higher after exposure to both ENDS cue compared to neutral cue. No effect of cue on intention to quit smoking. Intention to remain abstinent. Effects on smoking urges is inconsistent with previous research, raising questions about the ability to assess craving in online settings. | SC; G |

(Continued)
Table 1. (Continued)

| REF | POPULATION (N) | STUDY DESIGN | ENDS GENERATION / TYPE (MG/L NICOtINE) AND BRAND | RESEARCH QUESTION(S) | PRIMARY OUTCOME | SECONDARY OUTCOMES | CUES TYPE AND VISUAL METHODS | MEASUREMENTS | RESULTS | ROB AND SQ |
|-----|----------------|--------------|-----------------------------------------------|----------------------|----------------|-------------------|---------------------------|-------------|---------|------------|
| Maloney and Cappella | Smokers: Daily (N=301), intermittent (N=272) and former (N=311) smokers (total N=884) | Between subject 3 (cue: ENDS commercial with visual cue of smoking or vaping, commercial without visual cue, control) x 1 design for 3 groups (smoking status: daily vs intermittent vs former) x 1 design | | 1. Does exposure to vaping cues in ENDS ads decrease daily and intermittent smokers’ (a) self-efficacy to quit smoking (b) attitudes towards quitting smoking and (c) behavioural intentions to quit smoking? 2. Does exposure to vaping cues in ENDS ads decrease former smokers’ (a) self-efficacy to continue abstaining from smoking (b) attitudes towards smoking abstinence and (c) behavioural intentions to continue abstaining? | Urge to smoke tobacco cigarettes. | Attitudes Towards the Behaviour. Intention to abstain from smoking (former smokers). Intention to quit smoking (smokers). Self-efficacy (for smoking cessation and continued abstinence) | Visual depiction of ENDS advertisements. 16 ENDS advertisements of 12 ENDS brands in 3 ENDS commercials with/without vaping visuals or to answer unrelated media use questions (the no-ad condition). Smoking cigarette and vaping cues: paraphernalia, indirect behaviours and smoking behaviours. Visual depiction of vaping The only factor included in all cue condition ads and was systematically eliminated in the no-cue condition. | Visual depiction of ENDS advertisements. Attention measure: answered a post-test questionnaire. Measurements: Self-reported nicotine dependence. Fagerstrom test. Baseline urge: 10 item urges. Attitudes towards quitting or abstaining. Former smokers’ intentions to continue abstaining. Smokers’ intentions to quit smoking cigarettes. Visual attention: Eye-tracking. | | |
| Garrison et al | Young adults (non-smokers) who ever-vaped or at risk of vaping (N=26) | Within-subject 5 (cue: sweet ENDS vs tobacco ENDS vs menthol cigarettes vs regular cigarettes vs control) x 2 (warning label: present vs absent) design | | Do youth show product preference for sweet/fruit vs tobacco flavoured ENDS? | Cue-reactivity: Preference for sweet/fruit vs tobacco ENDS; advertising for sweet/fruit. Flavours interference with ENDS health warnings. | Advertisements in MRI of sweet/fruit and tobacco flavoured ENDS; advertising for sweet/fruit; Flavours and control images of sweets/fruits/mints with no tobacco product. All ENDS ads depicted e-liquid container/ENDS; all cigarette ads depicted cigarette pack/cigarettes. ENDS ads were for sweet: candy/desserts and fruit flavour. Warning label: present/absent. | Advertisements randomly contained warning labels, and recognition of health warnings was tested post-scan. | | | L, G |

(Continued)
Within subject 2 (cue: 24 videos of first generation ENDS vs e-toothbrushes) × 2 (time: before vs after using ENDS) design fMRI scan (NA) (11.7 ng/ml increase in plasma nicotine concentration after 10 min use of own ENDS).

What are the subjective and neurophysiological responses to ENDS cues (compared to neutral cues)?

Craving (neural and behavioural)

Effect on self-reported urge to use own ENDS post exposure.

Video of ENDS (first generation) Types: Greensmoke, NJOY and Firelight Fusion and E-toothbrushes (control cue).

Visual attention to video in fMRI.

Measures: VAS for withdrawal symptom and urge to vape.

No difference in urge after cue exposure. Brain responses to salient cues is enhanced by recent ENDS use. Self-reported urge ratings pre exposure were higher than post exposure. The effect of ENDS use in reducing the urge to use ENDS appears larger than the effect of the video in increasing urge to use.

Brain activation not detection of cue-related activity in brain areas associated with cue reactivity, but it was greater during the presentation of e-cigarette videos than during neutral videos in other brain regions. Activation was lower during pre-use session than during the post-use session.

Subjective measures: liking and intent to try were highest for control images than sweet ENDS, and sweet ENDS were greater than tobacco ENDS.

**Table 1.** (Continued)
Substance Abuse: Research and Treatment

| REF | POPULATION (N) | STUDY DESIGN | ENDS GENERATION / TYPE (MG/Ml NICOtINE) AND BRAND | RESEARCH QUESTION(S) | PRIMARY OUTCOME | SECONDARY OUTCOMES | CUES TYPE AND VISUAL METHODS | MEASUREMENTS | RESULTS | ROB AND SQ |
|-----|----------------|--------------|--------------------------------------------------|----------------------|------------------|------------------|-----------------------------|---------------|---------|-----------|
| Vena et al. | Young adults Current (N = 62) and former (N = 20) smokers (total N = 82) | Within subjects mixed 2 (cue: water bottle vs ENDS-JUUL; within) × 2 (smoking status: former vs current smoker) design | Fourth (69 mg) SALT | Do fourth generation ENDS function as cues. | Desire to vape and smoke (in smokers and former smokers) post fourth generation ENDS cue exposure (JUUL) | Smoking behaviour, latency 63% chose to smoke. | JUUL (fourth generation ENDS) and water bottle. | In person exposure observation of JUUL, 8 10 used by a study confederated with hand-to-Mouth movements (5 min tasks). Measures: Pre and post cue exposure. 3 VAS for desire for a tobacco cigarette (preferred brand) an ENDS and a JUUL. Brief questionnaire for smoking urgess. | For smokers, JUULs cues induced smoking urge and desire for smoking cigarettes and ENDS desire (MOD Pen and JUUL). Smoking latency: 63% chose to smoke. Former smokers: JUUL cue exposure increased desire for smoking tobacco cigarette and JUUL (modest and transient). JUUL did not produce smoking urge or desire for mod/vape pen. | L: G |
| Vena et al. | Young adult smokers (N = 64) | Mixed within and between-subjects 2 (cue: water bottle vs ENDS; within) × 2 (participant gender; between) design | Third (12 mg) | Do female-branded ENDS induce higher urge to smoke (conventional cigarettes or ENDS) in women than in men? | Smoking urge, cigarette and ENDS desire and smoking behaviour among women (vs men) smokers, after passive exposure to use of a female-marketed ENDS product selectively enhanced | Latency: ability to refrain from smoking vs obtaining a monetary reinforcement. 68% of men and 58% of women opting to smoke (vs. obtaining monetary compensation). | Mod device. Hot pink-coloured iStick Pico adorned with a jewelled crown or bow charm (VaporDolls, Etsy). E-liquid: 12 mg (Pacific Engineering Concepts), and either menthol or tobacco (according to participant’s preference). | In person exposure observation: Smokers observed a confederate drinking bottled water (control cue) and then vape a female-marketed tank-based ENDS (active cue). 8-10 hand-to-Mouth movements during 5 min tasks. Measures: Brief Questionnaire of Smoking Urges (BQSU) and visual analogue scales (VAS) for cigarette and ENDS desire pre- and post-cue exposure. Smoking latency task. | Exposure to cue increased desire and urge for both ENDS and conventional cigarette compared to the control cue; both 5 and 20 m after exposure. No effect of gender. | L: G |

(Continued)
| REF     | POPULATION (N) | STUDY DESIGN | ENDS GENERATION / TYPE (MGML NICOTINE) AND BRAND | RESEARCH QUESTION(S) | PRIMARY OUTCOMES | SECONDARY OUTCOMES | QUES TYPE AND VISUAL METHODS | MEASUREMENTS | RESULTS | ROB AND SQ |
|---------|----------------|--------------|--------------------------------------------------|----------------------|------------------|-------------------|---------------------------|---------------|---------|------------|
| Vena et al \(^7\) | Young adult smoker (N=50) | Mixed 2 (cue: ENDS vs water bottle; within) × 2 (smoke: normal vs enhanced; between) design | | 1. Do ENDS cues trigger smoking urges (vs. control cues). 2. Do enhanced 'smoke' clouds cue vaping desire? | Urge and desire for cigarette and ENDS. (Cue relativity to enhanced aerosol clouds on ENDS cue) | NR | ENDS mod containing e-liquid with either high (73%) or low (0%) vegetable glycerine (VG) | In person exposure: Participants observed a study confederate drinking bottled water and vaping an ENDS mod containing e-liquid with either high (73%) or low (0%) VG. Measures: Brief questionnaire on smoking urges (BQSU) and visual analogue scales (VAS) assessing cigarette ENDS desire pre- and post-cue exposure. | Exposure to ENDS enhanced clouds cue increased desire and urge for both ENDS and conventional cigarette compared to the control cue. Enhanced smoke clouds as well as regular smoke clouds increased cigarette and ENDS desire. | L; G |
| King et al \(^7\) | Young adult smokers (N=60) | Between subject 2 (cue: ENDS vs cigarette) × 1 design | | Does passive cues elicit smoking urge as much as exposure to a cigarette? | Desire and urges for tobacco cigarettes in passively exposed smokers to ENDS cues. | NR | NJoy King-ENDS similar to a tobacco cigarette. Tobacco cigarette (American Spirit or Benson and Hedges) (active cues) Bottled water (control cue) | In person exposure observation: Participants engaged in conversation with study confederate while he/she was drinking bottled water and then smoking either a combustible or ENDS. Measures: Subjective ratings (smoking desire and urge) pre and post cues exposure. VAS use for DESIRE of ENDS and tobacco cigarettes. Brief Questionnaire for Smoking urge (BQSU). | Passive exposure to both ENDS and conventional cigarettes increased desire and urge to smoke a regular cigarette. Exposure to ENDS cue (but not conventional cigarette) increased desire for ENDS. For all participants, desire ratings for a regular cigarette were higher than for an ENDS. | L; F |

(Continued)
| REF | POPULATION (N) | STUDY DESIGN | ENDS GENERATION / TYPE (MGML NICOTINE) AND BRAND | RESEARCH QUESTION(S) | PRIMARY OUTCOME | SECONDARY OUTCOMES | CUES TYPE AND VISUAL METHODS | MEASUREMENTS | RESULTS | ROB AND SQ |
|-----|----------------|--------------|-------------------------------------------------|-----------------------|-----------------|-----------------|------------------------|--------------|---------|-----------|
| King et al 74 | Young adult smokers (N = 108) | Randomised | Between subject 2 (cue: ENDS vs tobacco cigarette) × 1 design | Does passive exposure to ENDS that do not look like a tobacco cigarette elicit smoking/vaping urge as much as a conventional cigarette? | Cue reactivity for smoking/vaping urge to second generation ENDS | Smoking latency: Ability to refrain from smoking vs obtain a monetary reinforce. | Active cues: Second generation ENDS PEN (eGo device, 10 mg nicotine Juice e-liquid, flavour) | In person exposure observation: to engage in conversation with study confederate while he/she drank bottled water and then smoking either a tobacco cigarette or ENDS | Both ENDS and conventional cigarette increased smoking urge and desire. In addition, both ENDS and cigarette increased ENDS desire. These effects were independent of previous ENDS use. | L; G |
| King et al 75 | Young adult smokers (N = 78) | Randomised | Mixed: First-second (NA) | Can video imagery of ENDS elicit smoking urge and desire? | Change from pre-exposure baseline in smoking urge and desire for a combustible and an ENDS. | Active cue: video of ads of use of ENDS. ENDS in videos: First generation: Blu®, MyJoy® and Green Smoke® (82% of total video time). Second generation: eGo® (18% of total video cue time). | Video exposure of use of ENDS and neutral cue (bottled water). Measures: Pre and post exposure. Brief Questionnaire of Smoking Urges. Visual analogue scales: desire for a combustible and an ENDS. | Exposure to ENDS increased desire for ENDS as well as desire and urge for tobacco cigarette. | L; G |
| King et al 76 | Young adult smokers (N = 43) | Randomised | Between subject 2 (cue: ENDS video advertisements vs water video advertisements) × 1 design | Do second generation ENDS generalise as a conditioned cue to evoke smoking urge? | Cue reactivity of in-vivo passive exposure to ENDS (vape pen) use compared to conventional cigarette smoking. | Passive exposure to ENDS and tobacco cigarette cues in mood. ENDS observations did not affect mood. Tobacco cigarettes had a negative effect (increase bad mood, decrease good mood). | ENDS (Vape pen) and tobacco cigarette. | In person exposure observation: to engage in conversation with study confederate while he/she vaped either a combustible or ENDS (active cue). Measures: Brief questionnaire of smoking urges (BQSU) and 2 VAS: desire for a conventional cigarette (participant's preferred brand) and desire for an ENDS. Diener positive and negative mood scale. | Passive exposure to ENDS increased desire for ENDS and urge for tobacco cigarettes. Passive exposure to ENDS use, but not smoking tobacco cigarette, increased desire for ENDS, also it did not affect mood. Observation of smoking conventional cigarettes decreased positive mood. | SC; P |
Table 1. (Continued)

| REF | POPULATION (N) | STUDY DESIGN | ENDS GENERATION / TYPE (MG/ml NICOTINE) AND BRAND | RESEARCH QUESTION(S) | PRIMARY OUTCOME | SECONDARY OUTCOMES | CUES TYPE AND VISUAL METHODS | MEASUREMENTS | RESULTS | ROB AND SQ |
|-----|----------------|--------------|---------------------------------------------|----------------------|-----------------|-------------------|---------------------------|---------------|---------|------------|
| Dawkins et al,77 | Smokers (N=63) | Between subject 2 (ENDS colour: red vs white) × 2 (ENDS experience: none vs some) design | First (18 mg) | Does cigarette-likeness in ENDS cue increase craving? | Craving reduce and withdrawal symptoms for tobacco cigarettes after ENDS cue exposure. | NR | Tobacco flavour rechargeable ENDS-E-lites | Use of ENDS: 10, 3 s puffs of 18 mg/ml nicotine. Measures: Current craving: urge to smoke nicotine withdrawal symptoms: Mood and Physical Symptoms Scale; Pre and post exposure. | Only those who never used ENDS before had a lower craving for the red (ie, un-cigarette-like) ENDS; for previous ENDS users no difference in cues. | L; G |
| Jo et al,83 | Smokers (N=2201) | Randomised. Between subject 2 (message on ubiquity of ENDS: explicit vs implied) × 2 (ENDS visual cue: present/absent design) | NR (NA) | Do ENDS ad (implicit) message and/or visual cues affect smoking urge and behaviour? | Smoking cessation intention. Smoking urges and immediate smoking behaviour. | No effect of smoking behaviour | ENDS paper fixed ads: 2 MarkTen and 2 Fin ads. Cigalike ENDS in various context: bar, restaurant. Indoors/outdoors being use by a person. 2 presence/absence of ENDS cue. 2-message form: implicit or explicit ENDS use anywhere. | Visual exposure to ENDS varied advertisements Measures: Quit smoking intention: 3 items (post exposure) Mediating variables: 2 items. Secondary outcomes: Questionnaire for smoking urges: 10 items Behaviour: 1 item. | Implicit message evoked higher smoking urge and in turn leading greater cessation intention. No effect of cue. No effects for smoking behaviour. | L; G |
| Dowd and Tiffany,78 | Dual users (N=54) | Within subject 3 (cue cigarette vs ENDS vs water) × 1 design | First to fourth of personal ENDS and liquid own liquid (NS); | Does cue exposure enhance craving and spending behaviour for cue specific nicotine products or both products? | Cue-specific reactions to tobacco and ENDS with a primary focus on evaluating the relative reward value of both forms of cigarettes. Money willingness to spend to access the cue. Participants spent significantly more to access tobacco cigarettes than e-cigarettes. | It conventional cigarette, own ENDS Cup of water (in multiple trials). | Choice Behaviour Under Cued Conditions procedure (CBUCC). Measures: Smoking and ENDS craving. Brief Questionnaire of smoking urges and cigarette Dependence index (both ENDS and tobacco cigarettes). Latency to access cue, spending choice time and consumption. | Significant craving and spend of money on tobacco cigarettes and ENDS trials than on water trials. Tobacco craving was higher than ENDS craving (in all trials). In cross-analysis, tobacco cues reduced craving for ENDS, but ENDS cues did not reduce craving for tobacco. | SC; F |
| REF          | POPULATION (N) | STUDY DESIGN | ENDS GENERATION / TYPE (MG/ML NICOTINE) AND BRAND | RESEARCH QUESTION(S) | PRIMARY OUTCOME | SECONDARY OUTCOMES | CUES TYPE AND VISUAL METHODS | MEASUREMENTS | RESULTS | ROB AND SQ |
|-------------|----------------|---------------|----------------------------------------------------|----------------------|-----------------|-------------------|-------------------------------|--------------|---------|------------|
| De La Garza et al (79) | Smokers (N=7) Tobacco dependent | Within subject 4 visits, random 2 x 10 puff of own cigarette vs 16 mg nicotine ENDS vs 8 mg ENDS vs 0 mg ENDS design. VR-party and paraphernalia. | NR (16, 8 and 0 mg) Blue e-Cig. | Do ENDS have a different effect on craving and cue reactivity than regular cigarettes? To evaluate the effect of Blue ECs as compared to own cigarette, on: withdrawal (WSWS), craving (QSU) VR-induce reactivity (VAS craving) and smoking severity. | Craving and withdrawal responses in cigarette smokers to ENDS cues. | ENDS Rewards. Smoking severity ENDS dose-rewards: No reward feeling or matching the feeling of smoking own cigarette. Smoking severity: the time to first puff and number of cigarettes chosen in cigarette purchase task not significant. | Blue e-cigs (types not specified) Own tobacco cigarette VR-party and paraphernalia | In person use of ENDS (0, 8 and 16 mg/ml nicotine) or own cigarette. VR Cue exposure: party and paraphernalia cues. Measures: Assessment of withdrawal E-cig Questionnaire (post ENDS use). Craving (VAS) VR-induced cue reactivity (VAS) smoking severity | ENDS did not reduce smoking craving (QSU). Own cigarettes did. Between concentrations of ENDS nicotine: High nicotine liquid (16 mg) reduced ENDS withdrawal Vs 0 mg. All ENDS nicotine concentrations were not equally rewarding or matching the feeling of a conventional cigarette. VR Cue exposure did not show a difference in craving for cigarette after being exposed to smoking vs ENDS cues. | H: P |
| Tan et al (84) | Smokers (N=171) and dual users (N=122) (Total N=293) | Between subject 4 (message: anti-ENDS with vapour vs anti-ENDS without vapour vs pro-exercise vs anti-smoking) design | NR (NA) | Do vapour cues increase ENDS craving even in anti-vaping messages? | Cigarettes urge caused by vaping and smoking cues in PSAs. | Vaping and Anti-vaping intentions (Post exposure) and intention to purchase ENDS and traditional cigarettes (post exposure). Smokers: anti-vaping ad without vapour was associated with lower intention to buy ENDS and tobacco cigarettes. Dual users: Exposure to ad without vapour lower the intention to purchase ENDS. | 8 videos of Anti-vaping Public Services announcements (PSAs), with/without vapour, physical activity and visible smoking cues. | Exposure to videos with hand-to-mouth motion of using an ENDS, actors inhaled and exhaled visible emissions not visible. Measures: Perceived effectiveness of each PSA. Brief questionnaire of Smoking Urge and vaping urge (2 questions) Intention to smoke/vape in the next 1 (1 question) Intention to purchase tobacco cigarette/ENDS: Juster scale. | For smokers the anti-vaping ad with vapour cue was associated with lower intention to use ENDS and tobacco cigarettes and to purchase either as well as it was associated with lower intention to use ENDS (in the next hour). Exposure to ad without vapour was associated to lower ENDS urge and intention to by ENDS. | L: G |
| REF          | POPULATION (N) | STUDY DESIGN                  | ENDS GENERATION / TYPE (MGML NICOTINE) AND BRAND | RESEARCH QUESTION(S) | PRIMARY OUTCOME | SECONDARY OUTCOMES | CUES TYPE AND VISUAL METHODS | MEASUREMENTS | RESULTS | ROB AND SQ |
|--------------|----------------|-------------------------------|--------------------------------------------------|----------------------|-----------------|-------------------|-------------------------------|---------------|---------|----------------|
| Jo et al[85] | Smokers (N=3293) | Randomised: Between subject 2 (message on ubiquity of ENDS: explicit vs implied) × 2 (ENDS visual cue: present vs absent) design | NR (NA) | Do ENDS ad message and/or visual cues affect smoking cessation intention outcomes such as smoking urge and behaviour? | Smoking urges, and immediate smoking behaviour. No effects for smoking behaviour. | Printed ads for cigarette-like ENDS (cigalikes 2 MarkTen ads and 2 Fin ads). Presence/absence of visual ENDS cue. 3 messages: e-cigarette use anywhere, harm reduction, control message. | Online visualisation of prints of advertisements. Measures: Assessments of Quit intention (3 item scale) Brief Questionnaire of smoking Urge (post exposure). Smoking behaviour: 1 dichotomous question. | To quit intention and smoking urge (secondary outcome), there were no significant message or cue effects and no significant message by cue interactions. No effects for smoking behaviour. Messages of e-cigarette use anywhere and harm reduction were associated with lower odds of smoking during the experiment. | L; G |
| Van Heel et al[80] | Smokers (N=81) No previous vaping experience. | Between subject 2, 5 min session of use of ECs: either (nicotine content: 0 vs 36 mg) × 2 (sensimotor: handheld vs held by unipod) × 2 (visual: blindfolded vs not) × 2 (ENDS aroma: apple vs tobacco) | First (24 or 36 mg) 0 mg | What is the impact of nicotine content, sensimotor and visual feedback and ENDS aroma on craving for conventional cigarettes and ENDS? | Cravings for tobacco cigarettes and ENDS. | ENDS Fling’ model first generation sensimotor: handheld vs held by unipod visual: blindfolded vs not ENDS aroma: apple vs tobacco. Participants were given 3 try out ECs to use at home (1 wk then back to lab). | In person vaping (Lab session 5 min) following an abstinence period of 12 h. | Craving for conventional cigarettes and for ENDS went down during the experimental session (post ENDS use vs pre ENDS use); this effect was moderated by nicotine (which enhanced the decrease in craving). Non-nicotine cues (ie, visual and sensimotor) did not elicit craving. When participants were visually unrestricted, the nicotine group had a craving reduction from pre to post vape stronger than the non-nicotine group. | SC; P |
| Kroemer et al[81] | Occasional smokers (N=16) | Within subject 2 (nicotine content: 12 vs 0 mg) × 2 (flavour tobacco vs sweet) design | Second (12 mg; 0 mg) | Do sweet flavour enhance reward from ENDS flavours and nicotine effect? | Liking and wanting ratings and neural response. | 4 coloured e-cigarettes containing sweetened and unsweetened flavours with or without nicotine | Exposure period: 2 d per ENDS (8 exposure days) fMRI to assess brain responses to smell and sigh of 4 ENDS. Measures: VAS | Sweetness increases ENDS liking and brain cue-reactivity. Sweetness conditioned participants to like and want a flavour | L; F |

(Continued)
| REF | POPULATION (N) | STUDY DESIGN | ENDS GENERATION / TYPE (MG/ml NICOTINE) AND BRAND | RESEARCH QUESTION(S) | PRIMARY OUTCOME | SECONDARY OUTCOMES | CUES TYPE AND VISUAL METHODS | MEASUREMENTS | RESULTS | ROB AND SQ |
|-----|----------------|--------------|-------------------------------------------------|-----------------------|-----------------|-------------------|---------------------------|---------------|---------|------------|
| Dawkins et al(64) | Smokers with no ENDS experience (N=86) | Random allocated to: 3 ENDS: 18 or 0 mg (placebo) or holding an ENDS | First (18 mg, 0 mg) White super E-cigarette | Does the nicotine or the behaviour of ENDS reduce craving for tobacco cigarettes? | Effects of the White Super e-cigarette on desire to smoke, nicotine withdrawal symptoms. | ENDS effect in attention and working memory performance. The nicotine ENDS improved working memory performance compared with placebo. | White super e-cigarette (devices and cartridges supplied by The Electronic Cigarette Company) | In person, use of ENDS with/without 18 mg nicotine (ad libitum for 5 min) or just hold the ENDS. Measures: Fagerstrom Test of Nicotine Dependence. A single-item desire to smoke scale, and The Mood and Physical Symptoms Scale. A subset group completed the Letter Cancellation and Brown-Peterson Working Memory Tasks. | After 20 min, Both placebo and nicotine decreased desire to smoke. Anxiety, concentration and irritability only were reduced with nicotine. Smoke and withdrawal desire: baseline, vs 5 vs 20 min after 5 min ENDS use ad libitum. | L; F |
| Kim et al(62) | Current smokers (who had or are using ENDS) (N=519) | Regression on 5 DVs (awareness, thoughts on smoking, thought on quitting, urge to smoke, susceptibility to ENDS) by smoking status (dual vs smokers) | Blue eCigs (2013) NR (NA) | Does vaping status influence the effect of an ENDS advertisement? | Awareness of and receptivity to ENDS advert, cue exposure effect over smoking or quitting, urge to smoke and intention to try ENDS. | Cessation behaviour (attempt to quit smoking in the past and prior year). | A television advert of ENDS-blueCigs shown online. Actor vaping in everyday situations, exhaling clouds of vape. | Online visualisation of the tv ad of the blue eCigs. Measures: Awareness of and receptivity to ad. Frequency of seen ad in the past. How memorable, innovative or exited was ad developed. Likelihood of trying ENDS after exposure. Attempts to quit smoking ENDS use. | Smokers were aware and receptive to ENDS ad. Prior ENDS users and non-users were receptive to the ad. Viewing ad, elicited thoughts of smoking tobacco cigarettes and urge to smoke at the same time elicited thoughts of quitting tobacco cigarettes. Dual users were more receptive to ENDS cue. | L; F |

Abbreviations: NA, not applicable; NR, not reported; RoB, risk of bias; SQ, study quality. RoB indicators – L, low; SC, some concern; H, high. Quality indicators – G, good; F, fair; P, poor.
(ie, conventional tobacco cigarettes, ENDS or both) was obtained from the reviewed studies. The resulting findings are presented as follows.

Cue exposure to ENDS was found to enhance craving for conventional (tobacco) cigarettes in 10 studies,\textsuperscript{67,70-77,82} while eight studies reviewed did not demonstrate such a relationship.\textsuperscript{65,66,68,78,79,83-85} To ensure that this dichotomy was not the result of study quality or design, the groups were compared for whether studies had been conducted in person or online, their number of participants, year of publication, the generation of ENDS used and the quality or Risk of Bias assessment. No differences were found.

Cue exposure to ENDS induced craving for ENDS was found in 10 studies.\textsuperscript{66,68,70-76,78} Although Nichols et al\textsuperscript{69} investigated this, they did not find a significant result. However, this study had a relatively small sample size ($n = 7$) and, therefore, a low statistical power. In addition, while the results found in Dowd and Tiffany\textsuperscript{78} provided a clear indication of increased ENDS cravings to ENDS cue exposure, results did not establish whether ENDS increased cravings for conventional (tobacco) cigarettes (although it was found that ENDS did not reduce these cravings).

Cue exposure to ENDS induced cravings (desire and/or urge) for both conventional (tobacco) cigarettes and ENDS.\textsuperscript{70-76} Vena et al\textsuperscript{70} and Van Heel et al\textsuperscript{80} studied cue exposure to ENDS inducing craving reduction for both tobacco cigarettes and ENDS, and found significant results (moderated by nicotine).

\textbf{Is this response moderated by user smoking status?} Smoking status can play an important role in the way that a patient responds to ENDS cue exposure, in relation to attention and attitudes.\textsuperscript{65} In this study, smoking status was viewed in relation to both smoking conventional (tobacco) cigarettes and ENDS (dual users). Our findings in this regard are described next.

Most studies used participants who smoked tobacco, although the level of cigarette use varied between studies. Three studies specifically analysed non-smokers (either as a sample or as a subgroup of interest),\textsuperscript{66,68,69} three studies specifically targeted dual users,\textsuperscript{66,78,84} and two had exclusive ENDS users as a (sub) group.\textsuperscript{66,69}

With that caveat in mind, smoking status may play a moderating role. Comparing tobacco smokers to ex-smokers and non-smokers, current smokers spent more time looking at ENDS cues than the other two groups.\textsuperscript{65} In addition, this was the only group where ENDS cues elicited a smoking urge\textsuperscript{67} or craving for both cigarettes and ENDS.\textsuperscript{65} On the other hand, there is the analysis by Blackwell et al\textsuperscript{66} who carried out an online study comparing ENDS cue reactivity in current smokers and former smokers who were either daily vapers or non-vapers and found no influence of smoking status on cue reactivity (for either tobacco cigarettes or ENDS craving), which caused the authors to raise questions regarding the validity of online cue reactivity research. Nichols et al\textsuperscript{69} even reported no ENDS craving after exposure to ENDS cues for non-smoking ENDS users; yet as mentioned above, the sample in this study was small. Interestingly, Vena et al\textsuperscript{70} found that

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\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{flowchart.png}
\caption{Flowchart of the paper selection process.}
\end{figure}
ENDS cue exposure increased smoking urge and desire in current smokers, but only enhanced smoking desire (and not urge) in former smokers. However, the size of the latter group was considerably smaller (20 former smokers as opposed to 62 current), so statistical power may have been an issue.

Tan et al. compared the responses of exclusive tobacco smokers and dual users to vaping cues in anti-ENDS public service announcements. They found that for smokers, the ENDS cues lowered the intention to use ENDS or buy and smoke cigarettes, yet at the same time increased the urge to use ENDS or smoke (compared to no cue). Thus, the inclusion of a cue affected smokers’ rational acceptance of the advertisement’s message, but still automatically triggered the craving. No such effect was found for dual users.

Dowd and Tiffany studied dual users and found that cue exposure had to be matched to the type of dependency that it aimed to elicit: cigarette cues for tobacco craving and ENDS cues for eliciting ENDS craving. Within that design, cigarette cravings were stronger than ENDS cravings. Finally, Dawkins et al. reported an interaction between previous ENDS use and reaction to non-cigarette-like ENDS cues: participants who had previously used ENDS showed increased cravings for cigarettes regardless of whether the ENDS resembled a cigarette, while participants without ENDS experience only reported increased cravings after exposure to a cig-a-like ENDS.

Is this response moderated by ENDS generation or design? ENDS engineering and design has rapidly evolved in a short time. Many changes in capacity, duration and nicotine content have occurred in the devices since the first cig-a-like ENDS was marketed. The role of ENDS generation and design as a moderator in ENDS cue reactivity was an additional matter of interest in this review, and the results are as follows.

Overall, the reviewed studies were carried out between 2012 and 2020 and most of them used for their experiments, first and second-generation ENDS. Only two studies used exclusively third generation, and one study reported using fourth generation ENDS (JUUL) as a cue. Thus, two studies directly compared first and third generation ENDS and their respective effects on craving. No differences were found; both generations elicited craving to a similar extent. Comparing the results from studies that used exclusively first, second, or third generation ENDS, the only two studies that did not find cue reactivity used first generation devices. At the same time, two other studies using first generation devices did find an effect. Moreover, Nichols et al. had a small sample (n = 7) and Jo et al. compared craving after exposure to various ENDS advertisements; the control condition contained no visual image of ENDS but did state ‘Use Evermist E-Cigs’, all other conditions added either a visual cue, a more elaborate tag line, or both. No pre-exposure measures were taken, so it was not possible to say if all advertisements induced craving to the same amount, or if none produced any craving at all. King et al. examined the role of first and second generation ENDS design (similar/less-similar to conventional cigarettes), finding that both generation designs increased tobacco cigarette craving. Vena et al. used a fourth generation ENDS as a cue but asked participants to indicate their desire for a third and a fourth generation ENDS. They found that smokers reported an increased desire for both generations of ENDS, while former smokers only reported higher desire for fourth generation ENDS (JUUL), suggesting that generalisation may coincide with cue salience.

Further observations

Secondary outcomes. Secondary outcomes are a fundamental component of all systematic reviews. In this subsection, we include secondary outcomes pre-established in our review protocol as well as all those reported in the studies reviewed.

More than half of the studies (n = 15) investigated secondary outcomes, with some studies exploring more than one. Smoking latency, which relates to the participant’s ability to abstain from smoking tobacco cigarettes (measured in time) versus obtaining money as a reward, was determined in five studies. In studies developed by Vena et al., the majority of participants chose to smoke over the money compensation, and Dowd and Tiffany reported that participants spent more money to get cigarettes than ENDS. Additional secondary outcomes investigated in selected reviewed studies are presented next, including significant results on analyses: urge to vape, urge to smoke, intention to quit smoking or remain abstinent from smoking, desire to smoke and vape, self-efficacy (for smoking cessation and continued abstinence), intentions to smoke or vape, intentions to buy ENDS and traditional cigarettes. In this latter study, Tan et al. reported that anti-vaping advertisements without vapour was associated with lower intention to buy ENDS and tobacco cigarettes in the smokers group; and in dual users, the exposure to the advertisement reduced the intention to purchase ENDS. In terms of ENDS rewards, De La Garza et al. found that although a 16 mg/ml dose of nicotine though ENDS cue exposure (use) relieved withdrawal symptoms, it did not produce a rewarding feeling when compared to participants’ own tobacco cigarettes. Finally, in relation to the effect on mood, King et al. found that mood was negatively influenced by tobacco cigarette cue exposure. Additional related information is provided in Table 1.

Craving enhancing factors. Elements that intensify, increase or amplify the effect of a cue, can have significant influence in a person’s cue-reactivity. The ENDS industry has capitalised on this in marketing and, as such, understanding the use and effect of cue enhancing factors in patients’ cravings is paramount for future advances in ENDS cue-reactivity research. Relevant information gathered in this review in this regard is presented in this subsection.
Vena et al.22 found that artificially enhanced cues (e.g., a more pronounced smoke cloud) enhanced subjective cravings (for both cigarettes and ENDS) accordingly. Kroemer et al.81 found that sweet tasting e-liquids enhanced conditioning effects, that is, resulting in higher subjective craving at subsequent cue exposure. Moreover, sweet flavours enhanced the effect of nicotine on brain responses to ENDS cues (when paired with sweet and nicotine versus paired with either sweet or nicotine).81 Similarly, using functional Magnetic Resonance Imaging-fMRI, Garrison et al.68,69 found higher activation in the nucleus accumbens, a brain area associated with reward and addiction, after exposure to stimuli of fruit-flavoured ENDS rather than tobacco flavoured ENDS.

Craving reducing factors. Here we report the findings on craving reducing factors analysed in our systematic review. In accordance with previous studies developed in tobacco cigarette reducing factors analysed in our systematic review. In craving reducing factors.

After ENDS cue exposure (ENDS use), four studies69,77,79,80 reported that nicotine acted as a moderating factor in self-reported craving (urge or desire) reduction.64,69,79,80 De La Garza et al.79 found that 16 mg/ml-nicotine e-liquid reduced craving for ENDS but was not seen as equally rewarding as smoking tobacco. In particular, Van Heel et al.80 replicated these findings, reporting a reduction in craving for both cigarettes and ENDS after vaping, with a stronger reduction for using a nicotine-containing e-liquid (36 mg/ml) than a nicotine-free e-liquid. Nichols et al.69 found lower self-reported craving after controlled ENDS use, which was followed by an enhanced brain response to an ENDS cue (video). In this study, the effect of ENDS use in reducing the urge for e-cigarettes was larger than the effect of ENDS cue videos. Finally, Dawkins et al.64 found that both using nicotine-containing (18 mg/ml) and nicotine-free e-liquid reduced the desire to smoke compared to no ENDS use; however, only the nicotine e-liquid subsequently reduced anxiety and irritability, and improved concentration. In addition, the same authors reported that for smoking cessation, nicotine content appeared to be more important (acting as a moderator factor) for males than for females.

Discussion
The current systematic literature review set out to aggregate and evaluate the results from existing research on cue reactivity to electronic nicotine delivery systems (ENDS). Twenty-two studies were identified and analysed. While further research is needed to fully understand whether ENDS related cues increase craving for conventional cigarettes, most studies examined in this review agreed that they do enhance craving for ENDS. It was equally difficult to tell with certainty whether any relationship between ENDS cues and craving is moderated by smoking and vaping status.

Unsurprisingly, participants who have never smoked conventional (tobacco) cigarettes nor ENDS did not show reactivity to ENDS cues; yet at the same time there were no systematic differences in reactivity between dual users, exclusive smokers, or exclusive ENDS users found across the studies. It was noticeable that two studies used fMRI to investigate the brain response to ENDS cues in exclusively ENDS users69 and early vapers or those at risk of vaping.68 Although the results in the former were not significant, the latter show some interesting results in regards to neural responses to sweet/fruit flavours and users’ poor memory to warning labels. The relevance of these studies lies in the elimination of the effect of the tobacco cigarette smoker over the result, which could represent a clearer way to help understanding the complexity surrounding ENDS cue reactivity in ENDS users.

Furthermore, cue reactivity appeared remarkably consistent across ENDS generations. In this regard it is important to highlight that the majority of studies examined in this systematic review used first to third generation ENDS, and only two studies mentioned the use of fourth ENDS generation in their research, with one of them focussed on the JUUL cue exposure.70 First to third ENDS generation, generally do not hold the power and capacity that fourth generation ENDS do, including the nicotine concentration levels that these devices are designed to deliver. Further research and reviews focussed on fourth generation ENDS is needed, in order to better understand the effect that these powerful devices are having among ENDS users on nicotine dependence and their potential health implications. Taken together, these results suggest that ENDS cue reactivity generalises reasonably well across both cigarette smokers and ENDS users and device designs for ENDS craving. The use of enhanced stimuli (sweetness and enhanced smoke clouds) elicited an enhanced craving response. In addition, nicotine was the primary mediating factor for reducing craving. Although only four studies examined this, the findings align with previous reports for tobacco cigarettes.87 The therapeutic use of ENDS for tobacco cessation and replacement is an ongoing investigation and recommending it for these purposes requires sensible considerations.

In this review, secondary outcomes were a topic of interest of more than half of the studies examined. Latency to smoking cigarettes was the behavioural outcome most reported among many others explored, and according to the latency observations, participants had more cravings for tobacco cigarettes than ENDS, which may be associated to different factors, such as ENDS nicotine content, device used, smoking or vaping status or method of visualisation. More targeted and focussed studies are needed to help elucidating reasons behind this kind of results. According to the remaining findings, the role of ENDS cues in associated secondary outcomes are still quite unclear, but some of the results found may represent areas where future research efforts could be invested, such as the manipulation of ENDS characteristics (such as vapour clouds,
flavour, nicotine levels) towards reducing intentions to buy or use ENDS or conventional cigarettes and, in addition, the potential role of ENDS in helping to reduce withdrawal symptoms.

The consistency in findings regarding cue-induced cravings for ENDS is remarkable when one considers the vast differences in design that exist between the generations. The earlier cig-a-likes look very different to the more recent pods; the latter of the two often bear more resemblance to a USB flash drive, a portable radio or a tape roller than something that would traditionally dispense nicotine. This consistency could be considered relevant, as the scientific community would be hard-pressed to keep their knowledge up-to-date with every new design that is released. Instead, this ease of generalising may imply the strength of the learned response.

Limitations

Two types of limitations can be discussed: limitations that are to do with the literature itself, and limitations of this review. Regarding the limitations from the literature, not all of the studies included were considered to be of fair or good quality; similarly, in several studies, there were concerns regarding bias. To minimise the chance of those studies biasing our current outcomes, the authors checked their results against a sample that only contained papers deemed of high quality and low risk of bias, and no differences emerged in the findings. Thus, we do not think that including the studies of lesser quality introduced any problems.

Furthermore, few studies explicitly addressed the influence of user smoking status on ENDS cue reactivity. This appears to reflect the earlier image of ENDS: an alternative nicotine provider to conventional cigarettes. However, ENDS have long expanded on their role of nicotine replacement therapy and, consequentially, little is currently known about users who vape for reasons other than limiting their cigarette use. A similar statement can be made on the influence of device design, although this can still be indirectly observed as the more recent studies employ more recent generation ENDS. Thus, it appears that ENDS design has little effect on cues, but a formal experiment to confirm this was not warranted.

Addressing the second type of limitation: a universal issue with literature reviews is publication bias.88,89 Since the current topic is quite new, intuitively we suspect that this particular topic might have a relatively low bias here as both a null result (i.e., ENDS cues do not elicit cravings) as well as a non-null result would be considered intriguing.

Conclusion

As ENDS design and its user base continue to evolve, more research will need to be devoted to how an ENDS dependency may take shape. A starting point for this will likely be cue reactivity. The variability in ENDS designs and user cultures may pose a challenge for researchers trying to find the fundamental principles of ENDS dependency, although it is encouraging to find that so far ENDS design has had limited effect on whether cue reactivity was established. Future studies will need to determine whether such a generalisation can also be made across user types and could further expand on the types of cues.

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Author Contributions

MK: Conceptualization-Supporting, Data curation-Lead, Formal analysis-Lead, Methodology-Supporting, Validation-Lead, Writing-original draft-Lead, Writing-review & editing-Lead. MCVC: Data curation-Supporting, Formal analysis-Supporting, Validation-Supporting, Writing-review & editing-Supporting. SH: Conceptualization-Lead, Funding acquisition-Equal, Methodology-Lead, Project administration-Supporting, Supervision-Equal, Writing-review & editing-Supporting. MT: Conceptualization-Equal, Funding acquisition-Equal, Methodology-Supporting, Project administration-Lead, Supervision-Equal, Writing-review & editing-Supporting.

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