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Electronic cigarettes: assessing the efficacy and the adverse effects through a systematic review of published studies

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ABSTRACT

Background To investigate the efficacy and the adverse effects (AEs) of the electronic cigarette, we performed a systematic review of published studies.

Methods We selected experimental and observational studies examining the efficacy (as reduction of desire to smoke and/or number of cigarettes smoked and/or quitting or as reduction of nicotine withdrawal symptoms) and the safety of EC (AEs self-reported or clinical/laboratory). The following search engines were used: PubMed, ISI Web of Knowledge and Cochrane Controlled Trials Register.

Results Finally, six experimental studies and six cohort studies were included. In the prospective 12-month, randomized controlled trial, smoking reduction was documented in 22.3 and 10.3% at Weeks 12 and 52, respectively ($P < 0.001$ versus baseline). Moreover, two cohort studies reported a reduction in the number of cigarette/day (from 50 to 80%) after the introduction of the EC. 'Mouth and throat irritation', 'nausea', 'headache' and 'dry cough' were the most frequently AEs reported.

Conclusions The use of the EC can reduce the number of cigarettes smoked and withdrawal symptoms, but the AEs reported are mainly related to a short period of use. Long-term studies are needed to evaluate the effects of the EC usage after a chronic exposure.

Keywords e-cigarette, electronic device, efficacy, safety, smoking, tobacco

Background

Even today, cigarette smoking is a major public health concern, with a high rate of avoidable premature mortality. This smoking-related mortality decreases rapidly after quitting and the incidence of lung cancer, stroke, chronic lung disease and other cancer depends on the length of smoking abstinence.[1–3]

Although smoking cessation has a high protective value for health, it is known that ~80% of smokers who attempt to quit on their own, relapse within the first month of abstinence and only ~3–5% remain abstinent at 6 months.[1,4]

Currently, to increase the likelihood of quitting, several drugs are available, including nicotine replacement therapy (NRT), bupropion and varenicline. However, they may lack high levels of efficacy in real-life settings. Consequently, new approaches to quit smoking have been developed.[5–7]

Electronic cigarettes (ECs) are battery-powered devices that provide inhaled doses of nicotine and other additives to the user.[8,9] It is a device designed to vaporize a liquid solution of propylene glycol and/or vegetable glycerine, in which nicotine or other aromas may be dissolved. Nicotine is inhaled in the form of vapour produced by a battery-operated heating element (atomizer).[5,10]

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In the current scenario, this way for quitting is gaining more and more importance among smokers. Since they were first marketed, the ECs have been promoted as being more cost-effective, usable in any public place without restriction, socially acceptable than traditional cigarettes and also been marketed as smoking cessation aid.[8] In the last period, the context and the regulation about the restriction of EC use in public places and their sales changed, with a great variability by countries and between countries.[11] It is important to underline that, in some countries, it is not allowed in no smoking area and this may be a problem for people who are likelihood of quitting.

Recently, a web survey conducted in the USA reported that the EC is known by 57.9% of the population and the use of this device has increased from 3.3% (2010) to 6.2% (2011). Interestingly, 21.2% of current smokers have tried the EC in 2011 while in 2010 they were 9.8%.[8,10,12]

This issue is gaining attention in the scientific community both in Europe and USA and this is mainly due to the possible impact on public health. In the last years the EC, as a potential method to quit smoking, has been the object of new scientific researches. Therefore, an integration of all data available is strongly necessary, in order to reach stronger conclusions than those drawn from individual studies. A clear summary of the scientific evidence regarding the use of EC, as a method to quit smoking, is required. For this reason, we decided to perform a systematic review of published studies in order to investigate the efficacy and the adverse effects (AEs) of the EC.

Methods

To achieve the main purpose of the present study, we performed a systematic review according to the PRISMA statements.[13]

Data collection

Two researchers independently performed systematic searches of the scientific literature in order to identify eligible articles from PubMed, ISI Web of Knowledge, Scopus and Cochrane Controlled Trials Register, using the following keywords: 'electronic nicotine delivery system', 'nicotine device', 'electronic cigarettes', 'e-cigarettes', 'electronic cigarette smoking' until April 2014. All papers written in English were considered for our purposes.

Study selection

In the first stage, the researchers analysed the search results individually to find potentially eligible studies. The publications were sorted by title and abstracts and only eligible studies were selected for full-text review. During this stage, all irrelevant studies (lack of pertinence, studies on animals, data already found in other publications) were excluded (Fig. 1). In the second phase, both experimental and observational studies were selected. In particular, we selected studies that examined the efficacy of EC (in terms of reduction of desire to smoke and/or number of cigarettes smoked and/or quitting or in terms of reduction of nicotine withdrawal symptoms) and the safety of EC (AEs self-reported or clinical/laboratory measured after using EC).

Data extraction and study assessment

The researchers reviewed each eligible full text and extracted the required data. For each study, information about characteristics of the survey, study design, sample size, funding, efficacy (in terms of reduction of desire to smoke and/or number of cigarettes smoked) and/or AEs (self-reported or clinical/laboratory measured) were retrieved (Tables 1–3).

The methodological quality of the studies was assessed according to the NEWCASTLE – OTTAWA Scale (NOS),[24] a 8-item scale designed to rate the quality of the observational studies and to the JADAD Scale[25] that was specifically developed to assess the validity of the experimental studies.

Results

From the first step of the search, 480 articles were found. Of these, 27 were selected by title and abstract and, finally, after reading the full texts, 12 articles were reviewed (Fig. 1). Six studies were experimental studies,[5,14–18] whereas six were prospective cohort studies.[1,19–23]

Efficacy (reduction of desire to smoke and/or number of cigarettes smoked)

Experimental studies

Bullen *et al.* in 2010 published the results of a randomized cross-over trial aimed at evaluating the change in desire to smoke in 40 adult smokers. Participants were randomized in four branches to use EC (16 mg), EC (0 mg), nicotine inhalator or usual cigarette on each of four daily sessions with overnight smoking abstinence before use of each product. They showed that the desire to smoke ratings (number of cigarettes/day) reached the lowest level 5 min after the first puff with usual cigarettes and 15 min after first puff with EC 16 mg nicotine. During the period of 60 min, participants using the EC have experienced a significant decrease in the desire to smoke same equal to regular cigarette ($P < 0.01$).[14]

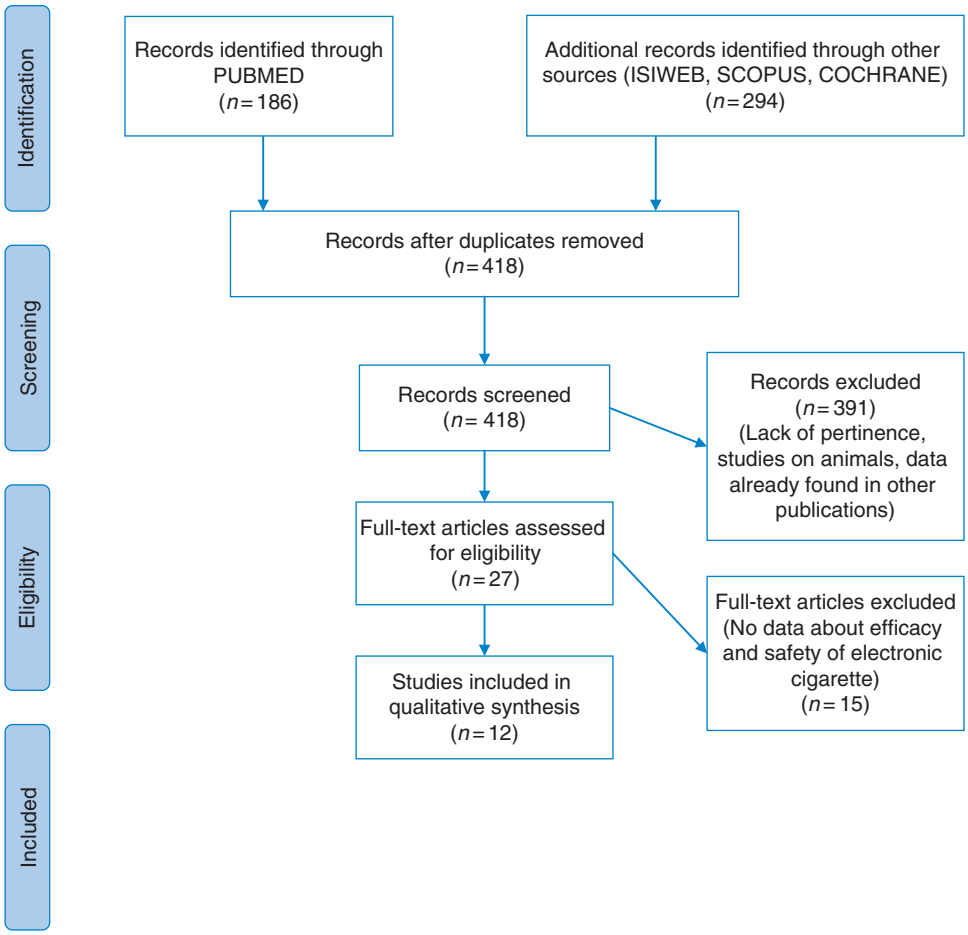

Fig. 1 PRISMA flow diagram (adopted from Moher *et al.*[13]).

The ECLAT Study (EffiCiency and Safety of an eLectronic cigAreTte)[5] is a prospective 12-month, double-blind, randomized controlled trial (RCT) designed to assess the efficacy and safety of EC loaded with 7.2 mg nicotine, 5.4 mg nicotine cartridges in comparison with no-nicotine cartridges (three arms). Evaluating smoking reduction/abstinence in 300 regular smokers using EC, the declines in cigarette/day use were observed in all three study groups (7.2–5.4–0 mg nicotine) with no consistent differences among study groups. Smoking reduction was documented in 22.3 and 10.3% at Weeks 12 and 52, respectively. Complete abstinence from tobacco smoking was documented in 11, 17 and 4% (respectively, in the three arms) at Week 12 and 13, 9 and 4% and Week 52 (respectively, in the three arms) ($P < 0.001$ versus baseline).

Dawkins *et al.*[15] randomly allocated 86 EC naïve smokers to either 18 mg nicotine, 0 mg nicotine (placebo) or just holding the EC in order to explore smoking reduction and abstinence related to EC use. After using the EC *ad libitum* for 5 min, the mean desire to smoke score significantly ranged from 4.5 (at baseline) to 2.5 20 min after use ($P < 0.05$).

The second study published by Bullen *et al.* in 2013,[18] a RCT, has documented a reduction of the mean cigarette consumption by two cigarettes per day more in the nicotine e-cigarettes group than the patches group ($P = 0.002$). The authors found that 57% of the e-cigarettes group reduced daily cigarettes by at least half at 6 months than in the patches group (41%; $P = 0.0002$) and in the placebo e-cigarettes group (45%; $P = 0.08$). An abstinence at 6 months after quit day of 7.3% in the nicotine e-cigarettes group, followed by the patches group (5.8%), and placebo e-cigarettes group (4.1%; $P = 0.44$) were observed. Moreover, the median time to relapse in the nicotine e-cigarettes group was 35 days, more than twice as long as in the patches group (14 days, $P < 0.0001$) or placebo e-cigarettes group (12 days, $P = 0.09$).[18]

Cohort studies

Furthermore, two cohort studies[1,23] reported a reduction in the number of cigarette/day (from 50 to 80%) after the introduction of the EC.

Table 1 Characteristics of the studies

Author	*Year*	*Country*	*Sample size*	*Study design*	*Length of the study*	*Funding*[a]
Experimental studies						
Bullen *et al.*[14]	2010	New Zealand	40	Randomized cross-over trial:randomly allocated to either: 16 mg EC, 0 mg EC (placebo) or nicotine inhalator or tobacco cigarette	Four study days 3 days apart.	Sponsored
Dawkins *et al.*[15]	2012	UK	86	Experimental study:randomly allocated to either: 18 mg EC, 0 mg EC (placebo) or just hold EC	Daily (*ad libitum* for 5 min)	No funding
Flouris *et al.*[16]	2012	Greece	30	Randomized cross-over study:three experimental sessions[b] (Sm: AS-CON, AS-TOB, AS-EC) (never sm: PS-CON, PS-TOB, PSE-EC)	Three sessions (30 min each) separated by 7 days of wash-out	No-profit
Vardavas *et al.*[17]	2012	USA	30	Experimental study:experimental group use the e-cigarette *ad libitum* for 5 min, control group use EC with similar frequency, but without the e-cigarette cartridge	Daily (*ad libitum* for 5 min)	No-profit
Caponnetto *et al.* Eclat study[5]	2013	ITA	300	Randomized controlled trial(RCT):three-arms double-blind, controlled, randomized, clinical trial: 7.2 mg nicotine, 5.4 mg nicotine, no-nicotine	52 weeks	Sponsored
Bullen *et al.*[18]	2013	New Zealand	657	Randomized controlled trial (RCT)Three parallel group, randomized controlled trial	6 months	No-profit
Prospective cohort studies						
Vansickel *et al.*[19]	2010	USA	32	Four Latin-square sessions differed by product: 1° EC 18 mg, 2° EC 16 mg, unlit cigarette	Daily (4 sessions each 150 min in duration each separated by 48 h)	No-profit
Eissenberg *et al.*[20]	2010	USA	16	Four Latin-square sessions differed by product: 1° EC 16 mg, sham smoking, 2° EC 16 mg nicotine, 3° EC 16 mg nicotine	Daily (4 sessions each separated by 48 h).	No-profit
Polosa *et al.*[1]	2011	ITA	40	EC 7.25 mg nicotine followed up prospectively for 6 months. They attended a total of five study visits: at baseline, Weeks4, 8, 12 and 24	6 months	Sponsored
Vansickel *et al.*[21]	2012	USA	20	First 'sampling' session (10-puff bouts), remaining three sessions randomly ordered 'choice' sessions that differed by the options provided (10 EC puffs, 10 OB puffs, money)	Four sessions (each 4 h)	No-profit
Vansickel *et al.*[22]	2013	USA	8	Session consisted of 4 EC smoking phases: baseline, 10 puffs (30-s interpuff interval), 1 h *ad libitum* and a 2 h no puffing	Daily (5 h session)	No-profit
Caponnetto *et al.*[23]	2013	ITA	14	A prospective (12 months) proof-of-concept study experimenting a popular brand of EC (7.4 mg nicotine)	52 weeks	Sponsored

[a]No funding, the study did not report any fund; no profit, the study was funded by a non-profit organization; sponsored, the study was funded by a profit organization.

[b]Sm, Smokers; AS-CON, control active smoking condition; AS-TOB, tobacco cigarette active smoking condition; AS-EC, electronic active smoking condition; never sm, never smokers; PS-CON, control passive smoking condition; PS-TOB, tobacco cigarette passive smoking condition; PSE-EC, electronic passive smoking condition.

Table 2 Results of the experimental studies

Author	*Efficacy reduction of desire to smoke and/ or number of cigarettes smoked*	*Efficacy reduction of nicotine withdrawal symptoms*	*Safety AEs or physiological effects*	*Safety physiological effects*
Experimental studies				
Bullen *et al.*[14]	Desire to smoke ratings (number of cigarettes per day) reached the lowest level 15 min after first EC puff. During the period of 60 min a significant decrease in the desire to smoke same equal to regular cigarette was observed ($P < 0.01$)	Anxiety, poor concentration, irritability and restlessness as nicotine withdrawal symptoms most compensated by using EC	Mouth (20.6%) and throat (32.4%) irritation, dry cough (32.4%), nausea (14.4%) were the most frequently AEs (short-term) reported by the EC smokers and diminished substantially	No data
Dawkins *et al.*[15]	After using the EC *ad libitum* for 5 minutes the mean desire to smoke score significantly ranged from 4.5 (at baseline) to 2.5 20 min after use ($P < 0.05$)	Nicotine withdrawal symptoms were significantly reduced 20 min after use especially in males who have tried the EC *ad libitum* for 5 min ($P < 0.001$)	No data	No data
Flouris *et al.*[16]	No data	No data	No data	CBC remained unchanged during active and passive e-cigarette smoking sessions ($P > 0.05$), in contrast tobacco cigarette smoking increased white blood cell, lymphocyte and granulocyte counts for at least 1 h in smokers and never smokers ($P < 0.05$)
Vardavas *et al.*[17]	No data	No data	No data	During short-term use, the e-cigarettes cause an increase of respiratory resistance similarly to tobacco smoking while the long-term effects are unknown
Caponnetto *et al.* ECLAT STUDY[5]	Smoking reduction was documented in 22.3 and 10.3% at Weeks 12 and 52, respectively. Complete abstinence from tobacco smoking was documented in 10.7 and 8.7% at Weeks 12 and 52, respectively. ($P < 0.001$ versus baseline)	Randomized patients reported withdrawal symptoms only occasionally	At baseline, the most frequently reported AEs were dry cough (26%; average for all study groups combined), mouth irritation (22%), shortness of breath (20%), throat irritation (17%) and headache (17%). For all the investigated AEs, compared with baseline, a significant reduction in frequency of reported symptoms was observed at week-52: dry cough (12% average for all study groups combined), mouth irritation (11%), shortness of breath (6%), throat irritation (13%) and headache (3%)	No data

Continued

Table 2 Continued

Author	Efficacy reduction of desire to smoke and/or number of cigarettes smoked	Efficacy reduction of nicotine withdrawal symptoms	Safety AEs or physiological effects	Safety physiological effects
Bullen *et al.*[18]	At 6 months, verified abstinence was 7.3% with nicotine e-cigarettes, 5.8% with patches and 4.1% with placebo e-cigarettes (risk difference for nicotine e-cigarette versus patches 1·51 (95% CI −2·49 to 5·51); for nicotine e-cigarettes versus placebo e-cigarettes 3·16 (95% CI −2·29 to 8·61). Achievement of abstinence was substantially lower than we anticipated, thus we had insufficient statistical power to conclude superiority of nicotine e-cigarettes to patches or to placebo e-cigarettes	Over 6 months, AUTOS scores in the e-cigarettes groups halved from baseline compared with a decrease of a third in the patches group (data not shown). The difference was significant (1·56, $P = 0·02$), but the difference between the nicotine e-cigarettes group and placebo e-cigarettes group was not significant (1·34, $P = 0·19$)	We identified no significant differences in adverse events, with 137 events in the nicotine e-cigarettes group, 119 events in the patches group and 36 events in the placebo e-cigarettes group	No data

Polosa *et al.* carried out a 24-week cohort study designed to assess the possible modifications in smoking habits (reduction and abstinence) of 40 regular smokers that used EC (7.25 mg nicotine cartridge) *ad libitum* throughout the day. In 13 of the 40 (32.5%) participants, the use of cigarette/day was reduced by 50% at the end of the study ($P < 0.001$). A reduction of 80% in the number of cigarettes smoked was observed in 5 of the 40 participants (12.5%; $P = 0.043$).[1] A similar reduction was found by Caponnetto *et al.*, who conducted a prospective cohort study (12 months) intending to monitor the possible modifications in the smoking habits of 14 smokers with schizophrenia. In this study, a reduction of 50% in the number of cigarette/day was observed in 7 of the14 and their median value of 30 cigarettes/day decreasing significantly to 15 cigarettes/day ($P = 0.018$). Additionally, sustained smoking abstinence at Week 52 was observed in 2 of the 14 (14.3%) participants.[23]

Efficacy (reduction of nicotine withdrawal symptoms)

Experimental studies

The efficacy of the EC is also evident in reducing nicotine withdrawal symptoms. Indeed, Dawkins *et al.*[15] in 2012 reported that the desire to smoke and some aspects of nicotine withdrawal were significantly reduced 20 min after the EC use, especially in males who have tried the EC *ad libitum* for 5 min ($P < 0.001$). Also the study by Bullen *et al.*,[14] a randomized cross-over trial enrolled 40 adult smokers, reported anxiety, poor concentration, irritability and restlessness as nicotine withdrawal symptoms most compensated by using EC. Finally, in the ECLAT study the randomized patients reported withdrawal symptoms only occasionally.

In the sample analysed by Bullen *et al.*[18] over 6 months, the Autonomy Over Smoking Scale (AUTOS) scores in the e-cigarettes groups halved from baseline compared with a decrease of a third in the patches group (data not shown). This difference was statistically significant (1.56, $P = 0.02$), but the difference between the nicotine e-cigarettes group and the placebo e-cigarettes group was not significant (1.34, $P = 0.19$).[18]

Cohort studies

Even in prospective cohort studies, the EC seems to reduce the withdrawal symptoms associated with smoking traditional cigarettes. In the two studies by Vansickel *et al.*, reporting results by a daily cohort study concerning the effects of EC, eight EC smokers completed a 5 h session (baseline, 10 EC puffs, *ad libitum* puffing period and no puffing). All participants' declarations such as 'Calm you down' 'Concentrate' as well 'Reduce your hunger for food' and 'Taste Good'

Table 3 Results of the prospective cohort studies

Author	*Efficacy reduction of desire to smoke and/or number of cigarettes smoked*	*Efficacy reduction of nicotine withdrawal symptoms*	*Safety AEs or physiological effects*	*Safety physiological effects*
Prospective cohort studies				
Vansickel *et al.*[19]	No data	'calm', 'concentrate', 'awake' and 'reduce hunger' raised significantly at all time after electronic smoking	No data	No data
Eissenberg *et al.*[20]		The EC decreased craving significantly after 5 min ($P < 0.05$)		
Polosa *et al.*[1]	In the sample analysed 13 of the 40 (32.5%) participants the use of cigarette/day was reduced by 50%, from an average of 25 to 6 cigarettes/day at the end of the study ($P < 0.001$). A reduction of 80% in the number of cigarettes smoked was observed in 5/40 participants (12.5%) ($P = 0.043$)	No data	Mouth (20.6%) and throat (32.4%) irritation, dry cough (32.4%), nausea (14.4%) were the most frequently AEs (short term) reported by the EC smokers and diminished substantially	No data
Vansickel *et al.*[21]	No data	'Calm you down' 'Concentrate' as well 'Reduce your hunger for food' and 'Taste Good' increased significantly following the 10-puff period, peaked following the *ad libitum* period and decreased after the rest period	No data	No data
Vansickel *et al.*[22]	No data	'Calm you down' 'Concentrate' as well 'Reduce your hunger for food' and 'Taste Good' increased significantly following the 10-puff period, peaked following the *ad libitum* period and decreased after the rest period	No data	No data
Caponnetto *et al.*[23]	50% reduction in number of cigarette/day is observed in 7/14 and their median of 30 cigarette/day decreasing significantly to 15 cigarette/day ($P = 0.018$). Sustained smoking abstinence at Week 52 was observed in 2/14 (14.3%) participants	No data	Mouth (20.6%) and throat (32.4%) irritation, dry cough (32.4%), nausea (14.4%) were the most frequently AEs (short term) reported by the EC smokers and diminished substantially	No data

increased significantly following the 10-puff period, peaked following the *ad libitum* period and decreased after the rest period.[21,22]

The other two US studies enrolled, respectively, 32 and 16 smokers to four sessions, characterized by the use of a different type of EC, to evaluate nicotine abstinence symptoms suppression.[19,20] In Vansickel *et al.*,[19] the use of the terms 'calm', 'concentrate', 'awake' and 'reduce hunger' by the enrolled subjects raised significantly at any time after electronic smoking. In Eissenberg *et al.*,[20] the EC decreased craving significantly after 5 min ($P < 0.05$).

Short-term adverse effects

Mouth (20.6%) and throat (32.4%) irritation, dry cough (32.4%) and nausea (14.4%) were the most frequently AEs reported by the EC smokers and diminished substantially.[1,14,23] The same AEs are reported by smokers enrolled in the trial ECLAT where before using e-cigarettes, at baseline, the most frequently reported AEs were dry cough (26%; average for all study groups combined), mouth irritation (22%), shortness of breath (20%), throat irritation (17%) and headache (17%). For all the investigated AEs, compared with baseline, a significant reduction in frequency of reported symptoms was observed at Week 52: dry cough (12% average for all study groups combined), mouth irritation (11%), shortness of breath (6%), throat irritation (13%) and headache (3%).[5] Finally, the RCT by Bullen *et al.*[18] identified no significant differences in adverse events between the three arms, with 137 events in the nicotine e-cigarettes group, 119 events in the patches group and 36 events in the placebo e-cigarettes group.[18]

Physiological effects

Two experimental studies have measured the physiological effects caused by EC. Flouris *et al.*[16] reported that the complete blood count remained unchanged during active and passive e-cigarette smoking sessions ($P > 0.05$), in contrast tobacco cigarette smoking increased white blood cell, lymphocyte and granulocyte counts for at least 1 h in smokers and never smokers ($P < 0.05$). During short-term use, the EC cause an increase of respiratory resistance similarly to tobacco smoking while the long-term effects are unknown.[17]

Methodological quality assessment

The six selected experimental studies were assessed according to the JADAD Scale. Only two study met all the criteria (total score ≥ 3).[5,18] The remaining four experimental studies were missing information on blinding.[14–16,25] Only two studies reported information on withdrawals.[5,14]

The six cohort studies, included in the systematic review, were evaluated according to the NOS. No studies met all items of the scale. Only two items, regarding the selection, respected the quality criteria in all studies.[1,19–23]

Discussion

Main finding of this study

The efficacy of EC, in terms of reduction of desire to smoke-number of cigarettes smoked and in terms of reduction of nicotine withdrawal symptoms, was the first outcome analysed in this systematic review. The secondary outcome was the safety of EC concerning the AEs self-reported or clinical/laboratory measured after using EC.

Regarding the efficacy of EC, we found that four experimental studies[5,14,15,18] and six cohort studies reported a reduction in the desire to smoke—number of cigarettes and/or withdrawal symptoms (assessed using the Fagerstrom Test of Nicotine Dependence and the Mood and Physical Symptoms scale).[1,19–23] Smoking reduction was documented in 22.3 and 10.3% of participants at Weeks 12 and 52, respectively. Complete abstinence from tobacco smoking was documented in 10.7 and 8.7% at Weeks 12 and 52, respectively ($P < 0.001$ versus baseline).[5] Moreover, 57% of the e-cigarettes group reduced daily consumption of cigarettes by at least half at 6 months and an abstinence of 7.3% at 6 months after quit day in the nicotine e-cigarettes group was observed.[18] In addition, two cohort studies reported a reduction in the number of cigarette/day (from 50 to 80%) after the introduction of the EC.[1,23]

In all studies that analysed the withdrawal symptoms, the EC decreased craving significantly after 5 min ($P < 0.05$) and 'concentrate', 'awake' and 'reduce hunger' raised significantly at all time after electronic smoking.[5,14,15,19–22] For all the investigated AEs, compared with baseline, a significant reduction in frequency of reported symptoms was observed at Week 52: dry cough (−14%), mouth irritation (−11%), shortness of breath (−14%), throat irritation (−4%) and headache (−14%). Moreover, in Dawkins *et al.*[15] the use of the EC seems to improve the performance of working memory evaluated by Letter Cancellation Task and Brown–Peterson Memory Test.

Ten of the twelve studies have analysed the smoking EC s for a limited period of time (a maximum of 6 months). Only in two studies by Caponnetto *et al.*,[5,23] one prospective cohort study and one RCT, the enrolled sample was studied for 52 weeks, representing today the first long-term results of EC. Additionally, it is important to report that the majority of the studies were non-profit and this finding remark that the EC use draws attention of the non-profit institutions.

What is already known on this topic

In the current scenario, substances developed to increase the likelihood of quitting are available, such as NRT, bupropion and varenicline but relapse within the first months of abstinence are often registered. The use of new devices, such as the EC, could be a useful way to improve the quitting rate but a clear evidence on the efficacy and safety related to the use of these products do not exist.

What this study adds

Our study adds a comprehensive view on the topic of the use of EC, but further researches are strongly recommended in order to reach more complete knowledge about the possible impact of these kind of devices.

Several studies are currently ongoing to evaluate the chemical composition of fluids used in the EC.[26] The nicotine concentration, the chemical additives and biological effects are currently the major topics of interest. Taken together, the well-known lethality of nicotine, variability in cartridge/vapour content suggest the necessity to better evaluate, regulate, label and package the EC and nicotine containing solution in a manner consistent with cartridge content and product effect.

To date, considering the smoking prevalence in general population and particularly in health professionals[27–30] the use of the EC seems to be a possible method to quit smoking, since it reduces the number of cigarettes smoked and withdrawal symptoms. Also a significant reduction in frequency of reported AEs is observed and mainly related to a brief period of use. Of course long-term studies, following a specific protocol such as the one recently published by Manzoli *et al.*,[31] are strongly required to evaluate the effects of the EC use after a chronic exposure and to obtain concrete evidence relating to health outcomes.

Limitations of this study

Our study has some limitations. First, we restricted the data collection only to papers written in English. Secondly, there are methodological limits of the included studies regarding the period of exposure and the type of EC used. Smoking the EC for just few hours do not allow enough time neither for assessment of delayed acute effects nor the potential of long-term use. Indeed, the results of some outcome measures might be influenced by sample size, longer-term use, different puffing profiles, other EC models and the user's previous experience with EC. Variability in product design may influence vapour content and chronic use and more intensive puffing may influence nicotine delivery.[19,20] Thirdly, three studies were limited to smokers not intending to quit, which may underestimate the reduction in desire to smoke and there was no period of familiarization with the products before use.[1,14,23] Polosa *et al.*[1] and Caponnetto *et al.*[23] reported a failure rate of participants to attend their final follow-up visit, respectively, 32.5 and 40%. In the majority of the included papers, the study design do not compare different types of smoking cessation, but mainly ECs with various nicotine dosages. Moreover, the risk of bias cannot be excluded because the assessment of withdrawal symptoms in the studies was not rigorous, evaluated at each visit not from a clinical point of view, but only by asking the participants about the presence/absence of symptoms.

Interestingly, there was a high proportion of studies' participants that failed to attend all the follow-up visits. For instance, the largest experimental study[5] reported a 40% of losses to follow-up. This could be due in part to technical problems of the device.

Lastly, another limitation is related to the limited number of studies with a randomized control design and the low number of patients enrolled, 1143 for the experimental studies and 130 for the cohort studies. It is necessary to promote further trials characterized by high sample size and greater homogeneity of the outcomes analysed. For this limitation, this working group was unable to perform the meta-analysis of the available data in the present work.

References

1 Polosa R, Caponnetto P, Morjaria JB *et al.* Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study. *BMC Public Health* 2011;**11**:786.

2 Doll R, Peto R, Boreham J *et al.* Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004; **328(7455)**:1519.

3 U.S. Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

4 Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction* 2004;**99(1)**:29–38.

5 Caponnetto P, Campagna D, Cibella F *et al.* EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLoS One* 2013;**8(6)**:e66317.

6 Fiore MC, Jaén CR, Baker TB *et al.* Treating tobacco use and dependence: 2008 update U.S. Public Health Service Clinical Practice Guideline executive summary. *Respir Care* 2008;**53(9)**:1217–22.

7 Casella G, Caponnetto P, Polosa R. Therapeutic advances in the treatment of nicotine addiction: present and future. *Ther Adv Chronic Dis* 2010;**1(3)**:95–106.

8 King BA, Alam S, Promoff G *et al.* Awareness and ever-use of electronic cigarettes among U.S. adults, 2010–2011. *Nicotine Tob Res* 2013;**15(9)**:1623–7.

9 US Department of Health and Human Services website (FDA). Summary of Results: Laboratory Analysis of Electronic Cigarettes Conducted by FDA. http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm173146.htm (November2013, date last accessed).

10 Etter JF, Bullen C, Flouris AD *et al.* Electronic nicotine delivery systems: a research agenda. *Tob Control* 2011;**20(3)**:243–8.

11 Capasso L, Gualano MR, Flacco ME *et al.* E-cigarette regulations in Italy: fluctuating and confusing. *Lancet.* 2014;**383(9932)**:1883.

12 Yamin CK, Bitton A, Bates DW. E-cigarettes: a rapidly growing Internet phenomenon. *Ann Intern Med* 2010;**153(9)**:607–9.

13 Moher D, Liberati A, Tetzlaff J *et al.* Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Ann Intern Med* 2009;**151**:264–9.

14 Bullen C, McRobbie H, Thornley S *et al.* Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tob Control* 2010;**19(2)**:98–103.

15 Dawkins L, Turner J, Hasna S *et al.* The electronic-cigarette: effects on desire to smoke, withdrawal symptoms and cognition. *Addict Behav* 2012;**37(8)**:970–3.

16 Flouris AD, Poulianiti KP, Chorti MS *et al.* Acute effects of electronic and tobacco cigarette smoking on complete blood count. *Food Chem Toxicol* 2012;**50(10)**:3600–3.

17 Vardavas CI, Anagnostopoulos N, Kougias M *et al.* Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. *Chest* 2012;**141(6)**:1400–6.

18 Bullen C, Howe C, Laugesen M *et al.* Electronic cigarettes for smoking cessation: a randomized controlled trial. *Lancet* 2013;**382**:1629–37.

19 Vansickel AR, Cobb CO, Weaver MF *et al.* A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiol Biomarkers Prev* 2010;**19(8)**:1945–53.

20 Eissenberg T. Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. *Tob Control* 2010;**19(1)**:87–8.

21 Vansickel AR, Weaver MF, Eissenberg T. Clinical laboratory assessment of the abuse liability of an electronic cigarette. *Addiction* 2012;**107(8)**:1493–500.

22 Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine Tob Res* 2013;**15(1)**:267–70.

23 Caponnetto P, Auditore R, Russo C *et al.* Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study. *Int J Environ Res Public Health* 2013;**10(2)**:446–61.

24 Wells G, Shea B, O'Connell J *et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analysis.* Oxford, UK, July 3–5, 2000.

25 Jadad AR, Moore RA, Carroll D *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;**17**:1–12.

26 Konstantinos E, Farsalinos MD, Polosa R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. *Ther Adv Drug Saf* 2014;**5(2)**:67–86.

27 Ficarra MG, Gualano MR, Capizzi S *et al.* Tobacco use prevalence, knowledge and attitudes among Italian hospital healthcare professionals. *Eur J Public Health* 2011;**21(1)**:29–34.

28 La Torre G, Kirch W, Bes-Rastrollo M *et al.* Tobacco use among medical students in Europe: results of a multicentre study using the Global Health Professions Student Survey. *Public Health* 2012;**126(2)**:159–64.

29 Gualano MR, Siliquini R, Manzoli L *et al.* Tobacco use prevalence, knowledge and attitudes, and tobacco cessation training among medical students: results of a pilot study of Global Health Professions Students Survey (GHPSS) in Italy. *Z Gesundh Wiss* 2012;**20(1)**:89–94.

30 Gualano MR, Bontempi C, Saulle R *et al.* Validation of the global health professions students survey questionnaire in Italy. *Italian J Public Health* 2011;**8(4)**:392–8.

31 Manzoli L, La Vecchia C, Flacco ME *et al.* Multicentric cohort study on the long-term efficacy and safety of electronic cigarettes: study design and methodology. *BMC Public Health,* 2013;**13**:883.