E-print version

https://doi.org/10.1093/ntr/nty047

Marianna Masiero, Claudio Lucchiari, Ketti Mazzocco, Giulia Veronesi, Patrick Maisonneuve, Costantino Jemos, Emanuela Omodeo Salè, Stefania Spina, Raffaella Bertolotti, Gabriella **Pravettoni, E-cigarettes May Support Smokers With High Smoking-Related Risk Awareness to Stop Smoking in the Short Run: Preliminary Results by Randomized Controlled.** Trial, *Nicotine & Tobacco Research*, Volume 21, Issue 1, January 2019, Pages 119–126.

Title: E-cigarettes may support smokers with high smoking-related risk awareness to stop smoking in the short run: preliminary results by randomized controlled trial

ABSTRACT:

Introduction: E-cigarettes may be positively used in tobacco cessation treatments. However, neither the World Health Organization nor the American Food and Drug Administration has recognized them as effective cessation aids. Data about the efficacy and safety of e-cigarettes are still limited and controversial.

Methods: This was a double-blind randomized controlled study. The main focus of this paper is on a secondary outcome of the study, that is the assessment of effectiveness and safety of e-cigarettes in achieving smoking cessation in a group of chronic smokers voluntarily involved in long-term lung cancer screening. Participants were randomized into three arms with a 1:1:1 ratio: e-cigarettes (Arm 1), placebo (Arm 2), and control (Arm 3). All subjects also received a low intensity counseling.

Results:

Two hundred and ten smokers were randomised (70 to nicotine e-cigarettes, 70 nicotine-free placebo e-cigarettes, and 70 to control groups). About 25% of participants who followed a cessation program based on the use of e-cigarettes (Arm 1 and Arm 2) were abstinent after three months. Conversely,

only about 10% of smokers in Arm 3 stopped**.** A Kruskal-Wallis test showed significant differences in daily cigarettes smoking across the three arms (K-W = 6.277, p =.043). In particular, participants in Arm 1 reported a higher reduction rate (M = -11.6441, SD = 7.574) than participants in Arm 2 (M = -10.7636, SD = 8.156) and Arm 3 (M = -9.1379, SD = 8.8127)

Conclusions: Our findings support the efficacy and safety of e-cigarettes in a short-term period. E-cigarettes use led to a higher cessation rate. Furthermore, although all participants reported a significant reduction of daily cigarette consumption compared to the baseline, the use of e-cigarettes (including those without nicotine) allowed smokers to achieve better results.

Implications: E-cigarettes increased the stopping rate as well as the reduction of daily cigarettes in participants who continued smoking. In fact, although all participants reported a significant reduction of tobacco consumption compared to the baseline, the use of e-cigarettes allowed smokers to achieve a better result. It could be worthwhile to associate this device with new ICT-driven models of self-management support in order to enable people to better handle behavioral changes and side effects. This is true for ready-to-quit smokers (such as our participants) but can also be advantageous for less motivated smokers engaged in clinical settings.

Introduction

In the 1980s, Peto and Doll[1] described the severe health consequences of smoking. Nevertheless, the tobacco epidemic is still growing, and quitting smoking is difficult for many people. Tobacco cigarette smoking is also widespread in high-risk groups, such as cancer patients,[2,3] cancer survivors,[4,5] and individuals affected by respiratory diseases such as asthma and chronic obstructive pulmonary disease.[6]

Currently, nicotine-replacement treatments (NRTs) (patches, gum, nasal spray, and inhalers) are used to support smoking cessation as a first-line treatment.[4] The use of NRTs allows smokers managing craving and withdrawal.[7] Research evidenced that NRTs may be considered effective cessation aids particularly when combined with behavioral counseling.[8] Nevertheless, low compliance is often a critical issue, since after a short period many smokers reduce or interrupt the use of NRTs,[4,9] thereby decreasing their efficacy. Consequently, NRTs based programs have high (around 93%) relapse rate within 6 months.[10]

Harrell and colleagues suggested that the low compliance and the high relapse rate drove the development of new devices.[11] In 2004, the e-cigarette was introduced as a new tool to support smoking cessation,[12] considered both safe and efficacious.[13] However, neither the World Health Organization nor the American Food and Drug Administration has recognized the use of e-cigarette an effective cessation aid.[14] In the UK however, a company recently obtained the authorization to sell them with the label "tobacco cessation device."[15] Actually, data about the efficacy and safety of e-cigarettes are still limited and controversial. Bullen and colleagues[16] conducted a randomized controlled trial on 657 smokers who were unmotivated to quit, comparing nicotine e-cigarettes, nicotine-free e-cigarettes, and traditional nicotine replacement treatments. At a 6-month follow-up, results showed a low effect of the e-cigarettes, especially when nicotine was not present. More specifically, the group with nicotine e-cigarettes had an abstinence rate less than an 8%. Conversely, the EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) study suggested that the use of e-

cigarettes increased the likelihood of quitting and reduced the expired carbon monoxide (CO) level of participants.[17] More recently, a longitudinal study on 2028 participants found that e-cigarettes helped people stop smoking when used consistently.[15] The cessation success rate was higher for long-term e-cigarette users (42.4%) than for non-users (14.2%) and short-term users (15.6%). Despite these interesting results, many settings in which e-cigarettes might be a useful tool have yet to be tested. For instance, there are no data on the use of e-cigarettes in high-risk groups, such as chronic smokers. All studies conducted from 2003 to 2016 were correlational or survey studies, or they were exclusively based on unmotivated participants.[17-21]

A second important issue relates to safety. Available studies have reported that there are no dangerous short-term side effects.[22,23] E-cigarettes seem to be less toxic than traditional cigarettes.[16,17] However, some evidence of potential toxicity has been seen in animal models.[22-25] In a study on mice, Sussan and colleagues[24] found that e-cigarettes produce an inflammatory response similar to the one observed in mice exposed to tobacco smoking.

The screening procedure can represent a "teachable moment" for smokers. For instance, Borondy Kitts and colleagues (2016) reported a significant difference in cessation rate between smokers enrolled in clinical screening for lung cancer (abstinence rate: 14.5%) compared to the general population (abstinence rate: 5-7%). The National Lung Screening Trial (NLST) reported similar data on 53452 subjects.[26] We believe this to be a serious gap in the literature. However, no previous studies have tested the use of e-cigarettes in smokers enrolled in screening programs.

The main aim of the present study was to assess the efficacy of the use of e-cigarettes in a tobacco cessation program with a group of chronic smokers (smoking 10 or more cigarettes daily for 10 years or more)[27-28] voluntarily involved in long-term lung cancer screening, using a randomized controlled trial. Secondly, we aimed to analyze the impact of e-cigarettes on respiratory symptoms (e.g., dry cough, shortness of breath, mouth irritation, and phlegm). Unlike most previous studies, the present work targeted a specific group of smokers, namely chronic smokers with a moderate to strong

92 motivation to quit. As shown by a different study, motivation is a crucial predictor of smoking
93 cessation behavior.[29] In fact, not all smokers enrolled in lung cancer screening want to quit, since
94 their participation may be related to the need to manage smoking-related risks, rather than trying to
95 stop smoking. For the aforementioned reasons, in the present study, the efficacy of e-cigarettes was
96 tested only on motivated (ready-to-quit) smokers.
97
98 This trial had as primary outcome the assessment of the impact of a three-month e-cigarettes program
99 to reduce smoking-related respiratory symptoms (dry cough, breath shortness, mouth irritation and
100 phlegm) as a consequence of reduced tobacco cigarette consumption. The secondary objectives
101 included the assessment of the success rate of smoking cessation attempts in the three groups, daily
102 smoking reduction and the monitoring of safety and toxicity during the study. The present work
103 illustrates data at 3 months, where the primary outcome was not already measured. So we focused
104 here on smoking stopping, smoking reduction and safety issues. We think that timely data publication
105 is important in this research area, since the need of efficacy and safety data about e-cigarettes is vital
106 for clinical and policy decision makers, especially in critical population like the one we considered
107 We hypothesised that e-cigarettes filled with nicotine liquids (arm 1) would be more effective than
108 placebo, nicotine-free e-cigarettes (arm 2) and the control group (arm 3) for smoking reduction and
109 that they would have no greater risk of side-effects.
110 This is the first randomized controlled trial assessing efficacy and safety in a motivated high-risk
111 population. The complete study protocol has been published elsewhere.[28] The present work illustrates
112 data at 3 months.
113 **Method**
114 **Study design and participants**
115 The study was a double-blind randomized controlled trial. The first randomization was on 30
116 September 2015, and the last follow-up was on 31 January 2016. The Ethical Committee of the

European Institute of Oncology approved the study. All enrolled participants complied and signed the informed consent form. The study was in accordance with the principles stated in the Declaration of Helsinki (59th WMA General Assembly, Seoul, 2008).

Procedure

A sample size of 210 participants was chosen to allow for smoking reduction rate assessment. Starting with the expected intrinsic motivation of participants, the study aimed to have at least 80% retention at 6 months and 70% at 12 months. Considering these figures, we expected to maintain a statistical power to detect a reduction of 5 cigarettes per day in our smokers (being the cigarettes per day mean about 20 in the COSMOS population). Thus, using a two-sided two-sample t-test with a significance level (alpha) of 0.05, a sample size of 49 participants per arm we expected to achieve 80% power to detect a mean reduction of 5 cigarettes/day between any of the two experimental arms and the control arm, assuming a mean consumption of 20 cig/day in the control arm and common standard deviation within group of 8.7.

Two hundred and ten smokers (132 male and 78 female) with a mean age of 62.8 (SD = 4.587) agreed to take part in the study.

Overall, the average age at which participants smoked their first cigarette was 17.4 years (SD = 3.681), and the number of daily smoked cigarettes was 19.38 (SD = 7.844). The mean value of the CO for ppm was 14.84 (SD = 6.094) (min: 3 ppm, max: 33 ppm). Participants were enrolled at the IEO within the COSMOS II (Continuous Observation of SMOking Subjects) screening program. COSMOS II enables early detection of lung cancer using a low-dose computed tomography (CT) scan and blood tests. The inclusion criteria of the COSMOS II program includes people aged 55 or over who have smoked an average of 10 cigarettes a day or more for at least the past 10 years. Consequently, all COSMOS II participants have a long smoking history and are at higher risk of developing a smoking-related cancer[30].

In addition to the general COSMOS II inclusion criteria, in the present study we considered further inclusion and exclusion criteria, as follows.

Inclusion criteria:

- Having smoked at least 10 cigarettes a day for the past 10 years;
- High motivation to stop smoking (High or Very High at the motivational questionnaire);
- Not enrolled in other smoking cessation programs.

Exclusion criteria:

- Severe cardiovascular and respiratory diseases;
- Use of psychotropic medication;
- Current or past history of alcohol abuse;
- Any use of NRTs or e-cigarettes.

The use of NRTs was assessed during the interview and smokers who were using NRTs or had used NRTs in the previous 6 months were excluded. The use of e-cigarettes was defined as smokers who had ever regularly used e-cigarettes for more than 1 week alone or in combination with tobacco cigarettes.

Randomization

A randomization list using a permuted block design (40 blocks of 6 subjects randomly assigned to 1 of the 3 treatment arms) had been previously prepared by an independent personnel unit and labeled with progressive numbers applied to the packaging containing e-cigarettes and liquid cartridges with or without nicotine (Arm 1 and Arm 2).

According to this procedure, participants were randomized among three arms:

Arm 1 (E-Cigarette and Support) (*n = 70*): Each participant received an e-cigarette kit and 12 10-mL liquid cartridges (8 mg/mL nicotine concentration) free of charge. Participants were asked to consume no more than 1 ml of the liquid a day. The daily usage of the e-cigarette was assessed via a monthly telephone interview (around 10 minutes) and a daily self-

assessment diary. During the first week, participants used e-cigarettes ad libitum, combined with smoking regular cigarettes. At the end of the first week, participants were solicited by the researcher to use only the e-cigarette for the next 11 weeks.

Arm 2 (Placebo and Support) (*n = 70*): Each participant received an e-cigarette kit and 12 10-mL liquid that did not contain nicotine (placebo condition) free of charge. Participants were asked to consume no more than 1 ml of the liquid a day. The daily usage of the e-cigarette was assessed by a monthly telephone interview (around 10 minutes) and a daily self-assessment diary. During the first week, participants used e-cigarettes ad libitum, combined with smoking tobacco cigarettes.

Participants of the two groups did not receive liquid again if they ran out before the end of the 11 weeks.

Arm 3 Treatment (Control/Support-Only) (*n = 70*): Participants in this group did not use e-cigarettes.

Participants in all arms also received a low-intensity telephone counseling that included interviews at weeks 1, 4, 8, and 12. The amount and the modality of counseling was equivalent across arms. The counselor provided information, supported participants' motivation, and helped them coping with possible roadblocks. Each phone call lasted about 10 minutes. The counseling was provided by the same trained psychologist. Additional information on the trial is published elsewhere.[31]

Measures

E-cigarette Kit

The VP5 electronic cigarettes kit was chosen. It offered a good quality/price ratio and proven reliability and safety. The e-cigarette (eGO-CE4 PIEFFE) included a rechargeable 900 mAh battery (at least 250 recharges) (3.3-4.2 working voltage), and the atomizer had a long wick with a capacity of 1.6 ml. It had a blue LED button, and it permitted about 800 puffs before the battery needed to be

recharged. Nicotine and nicotine-free liquids were produced by BioFumo, who fully collaborated with us in providing an ad-hoc product for this study. In fact, the liquid nicotine concentration (8 mg/mL) and packages used were not available for commercial use. The nicotine concentration was defined by the Pharmacy Division of the IEO, according to the average number of daily cigarettes smoked by the participants (at least 10 cigarettes a day), avoiding excessive doses of nicotine. The flavor of the liquid was tobacco, called "Tobacco 7 Foglie." The tobacco flavor was chosen in order to avoid or to reduce confounding effects connected to individual smell perception. Therefore, a flavor close to that of traditional cigarettes was chosen. An electronic cigarette kit was provided free of charge to all participants. The VP5 electronic cigarettes kit was given to participants at the baseline assessment. At this moment, it was assessed the previous usage of other cessation aids (not only NRTs and e-cigarette) during the last year.

Also, participants were asked to refer to dedicated personnel (by phone, email or on-site) for any issue that might arise in relation to e-cig use. In particular, they were explicitly invited to use only the liquid provided, without purchasing further charges and to return all the bottles at follow-up (whether used or not used) which had been delivered at the beginning. The researcher in charge explicitly asked participants to report any of their experiences (including issues or doubts) regarding liquid and e-cig use during counseling calls, and at follow-up in order to avoid the possibility that participants might use the e-cigarettes incorrectly.

Physical assessment

Level of CO: The exhaled CO was measured using the Micro+™ Smokerlyzer® (Bedfont Scientific Ltd), which has less than 5% H2 cross-sensitivity. According to clinical evidence, a value from 1 ppm to 5 ppm is considered within the normal limits.

Respiratory symptoms: Self-reported measures were used to assess respiratory symptoms such as cough, shortness of breath, mouth irritation, and phlegm frequency (e.g., "Have you had a cough in the last week?").

Abstinence: continuous smoking abstinence (self-reported abstinence over the previous month,).

The Leicester Cough Questionnaire (LCQ): a 19-item self-report questionnaire to assess the impact of an acute and chronic cough on quality of life, is composed of two subscales: physical and psychological.[32] The overall score ranges from 3 to 21, with higher scores indicating better quality of life.

Psycho-cognitive assessment

Fagerstrom Test for Nicotine Dependence: a 6-item self-administered questionnaire assessing nicotine dependence.[33]

Motivational questionnaire: a 4-item, self-administered questionnaire assessing motivation to quit. The total score enables classification of smokers into 1 of 4 motivational categories: 4-6 = low (not yet seriously considering giving up smoking); 7-10 = middle (the person evaluated both the benefits of quitting and the risks of smoking); 11-14 = high (there are moments in which the person is determined to quit smoking); 15-19 = very high (the person is ready to give up smoking). The total score classifies the patient into 1 of 4 motivational categories (from "not ready to quit" to "highly motivated").[34]

Hospital Anxiety and Depression Scale (HAD): a self-administered questionnaire composed of two 7-item scales (anxiety and depression scales), which can be used as two separate measures of emotional distress. The HAD evaluates symptoms of anxiety and depression, avoiding misattribution due to the physical components of the illness.[32] The HAD is a short self-report questionnaire used to assess both anxiety and depression. It was first targeted at hospitalized people because it avoids evaluating physical symptoms that may confuse depression with the consequences of a physical impairment. Now, it is widely used both in clinical and nonclinical populations. It was previously adopted in studies on smoking cessation.[35]

All the aforementioned measurements were recorded at baseline, 3 months, 6 months, and 1 year. Also, during the phone interviews (at weeks 1, 4, 8, and 12) the use of cigarettes and e-cigarettes

liquid per day have been monitored, as well as the use of other cessations aids. These variables were also used to check for any differences among arms at the baseline in order to verify homogeneity.

Data Analysis

Nonparametric statistics were used to compare groups. More specifically, a Chi-squared test was used to assess differences in respiratory symptoms, e-cigarette side effects, and any other categorical variables. Mann-Whitney U (for 2 samples) and Kruskal-Wallis H (for 3 samples) tests were used to evaluate statistical differences in cigarette consumption and frequencies of participants who stopped smoking. We opted for nonparametric tests since our measures were not normally distributed. As suggested by Sawilowsky and Clifford-Blair[34] (1992), the use of nonparametric statistics in these cases increases the likelihood of avoiding type II errors, preventing false negatives. Our aim was to minimize the risk of failure to detect the effect of the different treatments. All the analyses were performed with the SPSS package (version 23.0, IBM, USA, 2014).

Results

At the baseline, the levels of anxiety and depression were not significantly different between the three groups. Generally, participants reported normal values, indicating the absence of clinical depression. Likewise, no differences among groups were found in the physical and psychological domains based on the LCQ scores. Some common e-cigarette side effects were reported (see Table 1).

Table 1 here

At month 3, we collected complete data about 170 participants. No statistical differences in the number of missing data were present between arms ($\chi^2(2) = .835$, $p = .659$). Participants in Arm 1 and Arm 2 had a similar compliance in the use of e-cigarettes. In fact, considering the number of empty flacons they gave back at the end of the study we dind't find any significant difference, though

the placebo group used on average less liquid (Arm 1 M = 10.9 empty flacons; Arm 2 M = 9.8 empty flacons).

Across study arms, 20% of participants (N = 34) stopped smoking at month 3. The percentage was significantly higher in the nicotine (N = 15; 25.4%) and nicotine-free (N = 13; 23.4%) e-cigarette groups than in the control group (N = 6; 10.34%) ($\chi 2(2) = 4.899$, $p = .044$).

Next, we compared reduction of cigarette consumption in participants who had used e-cigarettes (Arm 1 and Arm 2) and those who only received counseling (Arm 3). The Mann-Whitney U test reported significant differences between conditions (e-cigarettes vs. control) at month 1 (U = 2.508, $p < .010$) and at month 3 (U = 2.130, $p < .022$). The use of the electronic device actually helped participants reduce daily cigarettes. At month 3, also the reduction rate showed interesting results. Participants in Arm 3 reported smoking an average of 10.034 cigarettes/day, while participants in Arm 1 and Arm 2 showed a lower consumption (7.671 and 9.091, respectively). However, while the difference between Arm 1 and Arm 3 was statistically significant, differences between Arms 1 and 2 and between Arms 2 and 3 were not.

Considering the mean difference in cigarette consumption between the baseline and month 3, the Kruskal-Wallis H test for 3 independent samples showed a significant difference among Arms 1, 2, and 3 (see table 2): Participants in Arm 1 reported a higher reduction rate (M = -11.644, SD = 7.574) than participants in Arm 2 (M = -10.763, SD = 8.156) and Arm 3 (M = -9.138, SD = 8.8127).

Table 2 here

However, excluding from the reduction analysis the participants who discontinued smoking, we failed to find any statistical difference, even though in Arm 1 we found the highest reduction (M = - 9.164 in Arm1; M = -8.262 in Arm2; M = -7.875 in Arm3).

Considering respiratory symptoms, a significant reduction in all conditions was found, probably due to the decreased number of daily cigarettes smoked by most participants, independent of study arms.

In particular, about 21.5% of participants reported a decrease in coughing, about 18.50% reported less catarrh, and about 14.5% reported an improvement in breathing.

Focusing on e-cigarettes tolerability, our participants reported few side effects (see table 3). In particular, at month 1 the most relevant complain was “burning throat”. It was reported by about 23% of participants using liquid containing nicotine (while only about 4% of participant reported the same complain using nicotine-free liquid). However, at month 3 we observed a drastic decrease of the symptom (see table 4). Cough was also reported at month 1 by about 10% of participants, both using nicotine and nicotine-free liquid. Also in this case, the symptom decreased during time.

Table 3 here

Discussion

In this study, we tested the efficacy of e-cigarettes as cessation treatment in a sample of chronic smokers involved in a screening program. Our main result is that the use of e-cigarettes helped participant stop smoking since about one-quarter of participants who followed a cessation program based on e-cigarettes (both with and without nicotine) and a low-intensity counseling were abstinent after three months. Conversely, about 10% of smokers stopped following a program based only on a low-intensity counseling.

Furthermore, e-cigarettes increased the reduction rate in participants who continued smoking. In fact, although all participants reported a significant reduction of daily cigarette consumption compared to the baseline, the use of e-cigarettes (including those without nicotine) allowed smokers achieving a better result. The few side effects reported, which were also reported in other studies,[36-39] were well managed by participants and showed no increase during the treatment. Consequently, our findings confirm the efficacy as well as the safety of e-cigarettes in a short-term period.

Although participants in Arm 1 generally achieved better results, the placebo condition was effectively as well, in some case leading to comparable outcomes. This result has not been described before and provides suggestions for potentially fruitful new lines of research.

Future studies should analyze costs and benefits related to the use of nicotine-free e-cigarettes in high-risk patients who smoke. In particular, the efficacy of combining clinical counseling and nicotine-free e-cigarettes for high-risk patients should be discussed. In our view, it could have pivotal implications in clinical practice. We believe that nicotine-free e-cigarettes might be a first-line choice, particularly for subjects who have severe diseases (for example, those with heart problems) and cannot use nicotine or receive other medical treatments. However, the lack of differences between nicotine and nicotine-free device effects on smoking might also be linked to the low dosage of nicotine we adopted. In fact, using a device working at 10 W with an 8 mg/mL nicotine concentration we obtained quite a low dosage (less than 0.1 mg per puff) with respect to the nicotine normally assumed daily by a chronic smoker[40]. This may explain why results in Arm 1 (nicotine e-cigarettes) and Arm 2 (nicotine-free e-cigarettes) are so similar. Increasing nicotine concentration probably may enlarge this difference, although we need targeted research to establish which protocol may optimize the risk/benefits ratio.

In conclusion, taking into consideration the perspective of personalized medicine, e-cigarettes based protocols associated with new ICT-driven models of self-management may be implemented to support people to better handle behavioral changes and side effects.[41-45] This is true for ready-to-quit smokers (such as our participants) but could also be advantageous for less motivated smokers engaged in clinical settings.

Limits of the Study

The number of initial dropouts, i.e., participants who explicitly declared the willingness not to continue within the first month (1 participant in Arm 1, 2 in Arm 2, and 6 in Arm 3) was particularly high in in the control group. It might suggest that motivation to participate to the study was related to the possibility of using the e-cigarettes rather than an actual willingness to stop smoking. During the

study we had some missing data (12.4% at month 1; 21.9% at month 2; 18.1% at month 3) that limit our results. Monthly, we monitored the use of e-cigarettes during the counseling calls and the follow-up to manage potential problems. However, we didn't assess systemically any quantitative measure about the actual use. For this reason, only qualitative considerations can be done about the different use of e-cigarettes between subjects in Arm 1 and Arm 2.

Furthermore, the number of smoked cigarettes was recorded as participants' self-reports, which might have led to a measurement bias. The impossibility of assessing carbon monoxide in an expired breath at month 3 because of the study design cannot disambiguate the aforementioned possible explanation. However, if present, this effect was constant in all 3 arms, thus not affecting the exhibited effects. Finally, this paper focused on a secondary outcome, since the primary one was supposed to be assessed at six months.

Protocol

Clinicaltrials.gov NCT02422914; https://clinicaltrials.gov/ct2/show/NCT02422914

Funding

This study was supported by a grant from Fondazione Umberto Veronesi (FUV).

Authors' Contributions

CL, MM, GP, PM, and GV conceived and designed the study. CL coordinated the study, CL and GP acquired legal authorizations, and MM, KM, and SS managed participants. Statistical analyses were provided by CL and KM, while data management was provided by RB. E-cigarettes and liquids were managed by JC and EOS. Drafting and writing of the manuscript were handled by MM, KM, CL, and GP. All authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Reference

[1] Doll R, Gray R, Hafner B, Peto R. Mortality in relation to smoking: 22 years' observations on female British doctors. *BMJ*. 1980;280(6219):967-971. PMCID: PMC1601142

[2] Berg CJ, Thomas AN, Mertens AC, et al. Correlates of continued smoking versus cessation among survivors of smoking-related cancers. *Psychooncology*. 2013;22(4):799-806. doi:10.1002/pon.3077.

[3] Masiero M, Riva S, Fioretti C, Pravettoni G. Pediatric Blood Cancer Survivors and Tobacco Use across Adolescence and Emerging Adulthood: A Narrative Review. *Front Psychol*. 2016;7:392. doi:10.3389/fpsyg.2016.00392.

[4] Lucchiari C, Masiero M, Botturi A, Pravettoni, G. Helping patients to reduce tobacco consumption in oncology: a narrative review. *Springerplus*. 2016;5(1):1136. doi: 10.1186/s40064-016-2798-9

[5] Salloum RG, Getz KR, Tan AS, Carter-Harris L, Young-Wolff KC, George TJ, & Shenkman, EA. Use of Electronic Cigarettes Among Cancer Survivors in the US. *Am J Prev Med*. 2016;51(5):762-766. doi: 10.1016/j.amepre.2016.04.015.

[6] Perret JL, Bonevski B, McDonald CF, Abramson MJ. Smoking cessation strategies for patients with asthma: improving patient outcomes. *J Asthma Allergy*. 2016;9:117-128. doi:10.2147/JAA.S85615.

[7] Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev 2008;1:1. doi: 10.1002/14651858.CD000146.pub3.

[8] Ferguson SG, Gitchell JG, Shiffman S, Sembower MA, Rohay JM, Allen J. Providing accurate safety information may increase a smoker's willingness to use nicotine replacement therapy as part of a quit attempt. Addict Behav 20111;36(7):713–716. doi.org/10.1016/j.addbeh.2011.02.002

[9] Balmford J, Borland R, Hammond D, Cummings KM. Adherence to and reasons for premature discontinuation of stop-smoking medications: data from the ITC Four-Country Survey. Nicotine Tob Res. 2011;13(2):94–102; doi.org/10.1093/ntr/ntq215

[10] Barbeau AM, Burda J Siegel M. Perceived efficacy of e-cigarettes versus nicotine replacement therapy among successful e-cigarette users: a qualitative approach. Addict Sci Clin Pract. 2013;8(1):5. doi: 10.1186/1940-0640-8-5

[11] Harrell PT, Marquinez NS, Correa JB, Meltzer LR, Unrod M, Sutton SK, ... & Brandon TH. Expectancies for cigarettes, e-cigarettes, and nicotine replacement therapies among e-cigarette users (aka vapers). Nicotine Tob Res. 2014;17(2):193-200. doi: doi.org/10.1093/ntr/ntu149

[12] Bullen, C., McRobbie, H., Thornley, S., Glover, M., Lin, R., & Laugesen, M. (2010). Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tobacco control*, *19*(2), 98-103

[13] Regan AK, Promoff G, Dube SR, Arrazola R. Electronic nicotine delivery systems: adult use and awareness of the 'e-cigarette'in the USA. *Tob. Control*. 2013;*22*(1):19-23. doi:10.1136/tobaccocontrol-2011-050044

[14] Healton GC. Tobacco Control: How Are We Doing? *Am J Public Health*. 2016;106(7):1164-1166. doi: 10.2105/AJPH.2016.303209

[15] Zhuang YL, Cummins SE, Sun JY, Zhu SH. Long-term e-cigarette use and smoking cessation: a longitudinal study with US population. *Tob Control*. 2016; 25(S1):i90-i95. doi:10.1136/tobaccocontrol-2016-053096

[16] Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, Walker N. (2013). Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet*, 2013;382(9905):1629-1637. doi:10.1016/S0140-6736(13)61842-5

[17] Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, Polosa R. 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. doi.org/10.1371/journal.pone.0066317

[18] Polosa R, Caponnetto P, Morjaria JB, Papale G, Campagna D, Russo C. 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. doi: 10.1186/1471-2458-11-786.

[19] Etter JF, Bullen C. A longitudinal study of electronic cigarette users. *Addictive Behaviors* 2014;39(2):491–4. doi.org/10.1016/j.addbeh.2013.10.028

[20] Grana RA, Popova L, Ling PM. A longitudinal analysis of electronic cigarette use and smoking cessation. JAMA Internal Medicine. 2014;174:812–813.doi:10.1001/jamainternmed.2014.187

[21] McRobbie, H., Bullen, C. R., Hajek, P., & Hartmann-Boyce, J. (2014). Electronic cigarettes for smoking cessation and reduction. *Cochrane Review*. 2014;12. doi:10.1002/14651858.CD010216.PUB2.

[22] Knight-West O, Bullen C. E-cigarettes for the management of nicotine addiction. *Subst Abuse Rehabil*. 2016;*7*:111. doi:10.2147/SAR.S94264

[23] Benowitz NL, Goniewicz ML. (2013). The regulatory challenge of electronic cigarettes. *JAMA*. 2013;310:685–686. doi:10.1001/jama.2013.109501

[24] Sussan TE, Gajghate S, Thimmulappa RK, Ma J, Kim JH, Sudini K, Pekosz A. Exposure to electronic cigarettes impairs pulmonary anti-bacterial and anti-viral defenses in a mouse model. PloS one. 2015;10(2):e0116861. doi.org/10.1371/journal.pone.0116861

[25] Gallus S, Lugo A, Pacifici R, Pichini S, Colombo P, Garattini S, La Vecchia C. E-cigarette awareness, use, and harm perception in Italy: a national representative survey. *Nicotine Tob.* 2014:1-8. ntu124. doi: 10.1093/ntr/ntu124.

[26] Borondy Kitts AK, McKee AB, Regis SM, Wald C, Flacke S, McKee BJ. Smoking cessation results in a clinical lung cancer screening program. *J Thorac Dis*. 2016;8(Suppl 6):S481-S487. doi:10.21037/jtd.2016.03.11.

[27] Reilly M, Delanty N, Lawson JA, FitzGerald GA. Modulation of oxidant stress in vivo in chronic cigarette smokers. Circulation, 1996:94(1);19-25. doi: oi.org/10.1161/01.CIR.94.1.19

[28] Bergström J, Eliasson S, Dock J. A 10-year prospective study of tobacco smoking and periodontal health. J. Periodontol. 2000:71(8);1338-1347. doi.org/10.1902/jop.2000.71.8.1338

[29] Cox LS, Wick JA, Nazir N et al. (2011). Predictors of early versus late smoking abstinence within a 24-month Disease Management Program. Nicot. Tob. Res. 2011;13(3):215–220. http://dx.doi.org/10.1093/ntr/ntq227

[30] Lucchiari C, Masiero M, Veronesi G, et al. Benefits of E-Cigarettes Among Heavy Smokers Undergoing a Lung Cancer Screening Program: Randomized Controlled Trial Protocol. Eysenbach G, ed. *JMIR Res Protoc.* 2016;5(1):e21. doi:10.2196/resprot.4805.

[31] Maisonneuve, P., Bagnardi, V., Bellomi, M., Spaggiari, L., Pelosi, G., Rampinelli, C., ... & Veronesi, G. (2011). Lung cancer risk prediction to select smokers for screening CT-a model based on the Italian COSMOS trial. *Cancer Prevention Research*, canprevres-0026.

[32] Birring S, Prudon B, Carr A, Singh S, Morgan M, Pavord I. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax*. 2003;58(4):339-343. doi:10.1136/thorax.58.4.339.

[33] Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict*. 1991 Sep;86(9):1119-1127. PMID:1932883.

[34] Marino, L. "La disassuefazione dal fumo: l'ambulatorio." *L'epidemia di fumo in Italia. Pisa: EDI-AIPO Scientifica*. 2000.

[35] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67(6):361-370. doi: 10.1111/j.1600-0447.1983.tb09716.x

[36] Mykletun A, Overland S, Aarø LE, Liabø HM, Stewart R. Smoking in relation to anxiety and depression: evidence from a large population survey: the HUNT study. Eur. Psychiatry, 2008;23(2):77-84. doi.org/10.1016/j.eurpsy.2007.10.005

[37] Sawilowsky SS, Blair RC. A more realistic look at the robustness and Type II error properties of the t test to departures from population normality. Psychol Bull. 1992:111(2);352. Doi: doi.org/10.1037/0033-2909.111.2.352

[38] Tammemägi MC, Berg CD, Riley TL, Cunningham CR, Taylor KL. Impact of lung cancer screening results on smoking cessation. *JNCI J Natl Cancer Inst.* 2014;106(6):dju084. doi:10.1093/jnci/dju084

[39] Borland R. Electronic cigarettes as a method of tobacco control. BMJ. 2011;343:d6269. doi:10.1136/ bmj.d6269.

[40] Wagener TL, Floyd EL, Stepanov I, Driskill LM, Frank SG, Meier E, & Queimado L. Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. Tobacco control. *Tob Control.* 2016(20). http://dx.doi.org/10.1136/tobaccocontrol-2016-053041

[41] Riva S, Camerini AL, Allam A, Schulz PJ. Interactive sections of an Internet-based intervention increase empowerment of chronic back pain patients: randomized controlled trial. *J. Med. Internet Res.* 2014;16(8):e180. doi: 10.2196/jmir.3474.

[42] Schulz PJ, Hartung U, Riva S. Causes, coping, and culture: a comparative survey study on representation of back pain in three Swiss language regions. PLoS One. 2103;8(11):e78029. doi:10.1371/journal.pone.0078029.

[43] Kondylakis H, Koumakis L, Genitsaridi E, Tsiknakis M, Marias K, Pravettoni G, Mazzocco, K. IEmS: A collaborative environment for patient empowerment. In Bioinformatics &

Bioengineering (BIBE), IEEE 12th International Conference on. 2012:535-540. doi:10.1109/bibe.2012.6399770.

[44] Lucchiari C, Pravettoni G. Cognitive balanced model: a conceptual scheme of diagnostic decision-making. J Eval Clin Pract. 2012;18(1):82-88. doi: 10.1111/j.1365-2753.2011.01771.x.

[45] Gorini A, Mazzocco K, Gandini S, Munzone E, McVie G, & Pravettoni, G. Development and psychometric testing of a breast cancer patient-profiling questionnaire. Breast Cancer. 2015(7):133. doi.org/10.2147/BCTT.S80014

[46] Kondylakis H, Kazantzaki E, Koumakis L, Genitsaridi I, Marias K, Gorini A, & Tsiknakis, M. Development of interactive empowerment services in support of personalised medicine. Ecancermedicalscience. 2014:8. doi:10.3332/ecancer.2014.400

503 **Table 1.** The table shows participants baseline values and the Kruskal-Wallis H test between arms

Descriptive statistics of **the sample characteristics**	**Arm1 (E-Cigarette** and Support) (*n=70*)	**Arm 2 (**Placebo) (*n=70*)	**Arm 3 (**Control/Support-Only) (*n=70*)	
	M(SD)	*M(SD)*	*M(SD)*	
Behavioral and Physical factors				
Starting age	17.5 (3.748)		16.9 (3.612)	17.7(3.680)
CO (ppm value)	15.2(5.275)	14.6(5.942)	14.6(6.993)	
LCQ				
Physical Domain	5.6(0.991)	5.3(1.237)	5.4(1.269)	
Phsycological Domain	5.5(1.161)	5.3(1.399)	5.4(1.437)	
Psychological factors				
FTND scoring	4.5(1.788)	4.4(1.878)	4.1(1.954)	
Motivational scoring	12.6(2.234)	13.3(2.808)	13.1(2.491)	
HAD				
Anxiety scoring	5.2(3.882)	5.7(3.927)	5.1(3.749)	
Depression scoring	3.4 (2.888)	3.1(2.646)	3.8(3.000)	
Daily cigarette				

Baseline	19.2(6.123)	19.6(8.300)	19.3(8.939)

504

505 **Table 2.** The table shows the number of daily tobacco cigarettes smoked at different evaluation points

Number of **tobacco cigarettes smoked**	**Arm1** **(**E-Cigarette and Support)	**Arm 2** **(**Placebo and Support)	**Arm 3** **(**Control/Support-Only)
	M(SD)	*M(SD)*	*M(SD)*
Baseline	19.2(6.123)	19.6(8.300)	19.3(8.939)
1 Month	7.3(6.123)	8.8(7.397)	10.4(6.768)
2 Month	7.2(7.200)	8.5(6.234)	9.5(7.892)
3 Month	7.6(7.545)	9.1(7.557)	10.1(6.058)
Reduction	-11.7(7.574)	-10.8(8.156)	-9.1(8.812)

506

507

508

509

510

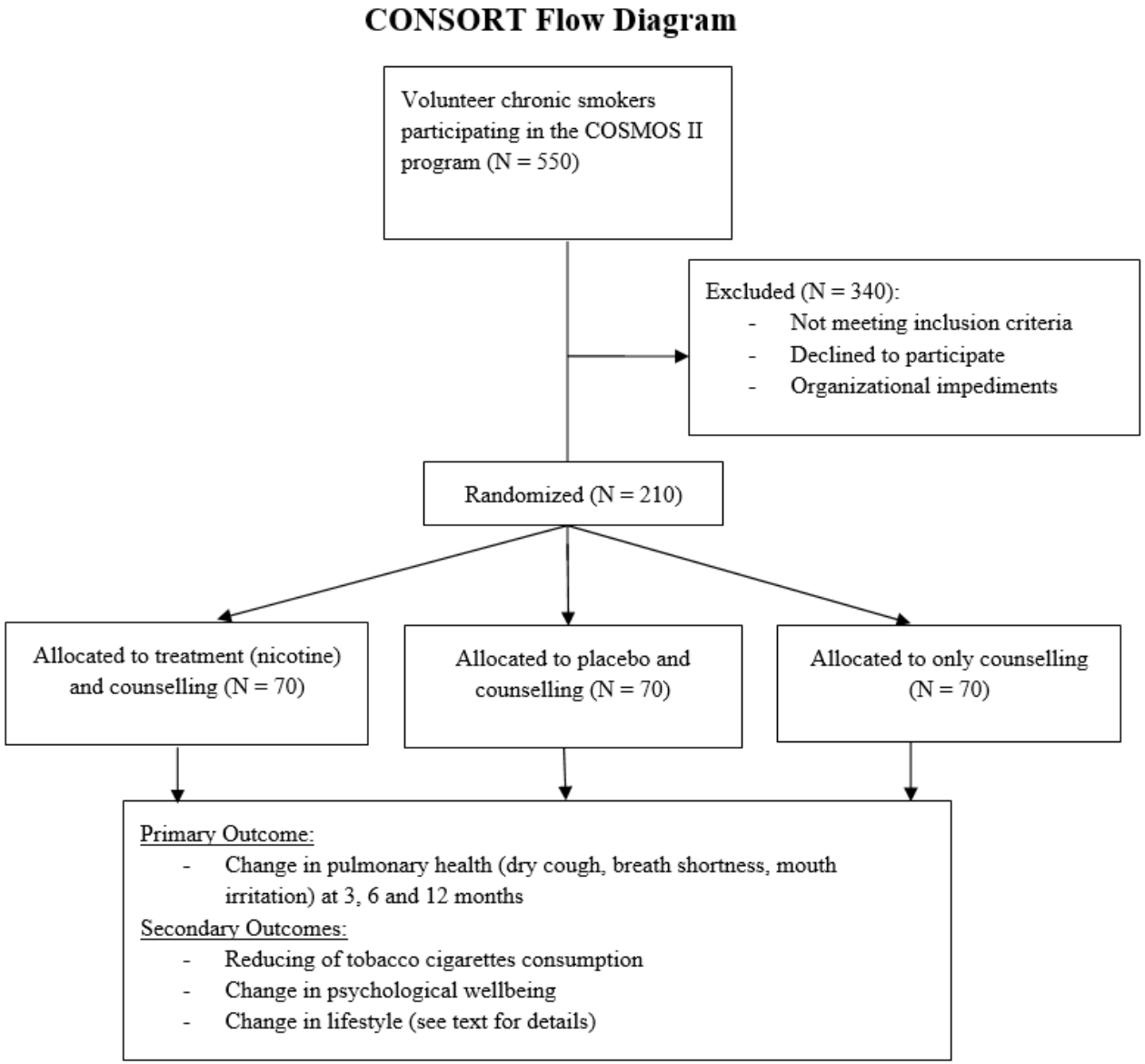
511

512 **Table 3.** The table shows main side effects of the e-cigarette at 1 and 3 months.

Table 1.1 **Side** Effects at 1 Month and 3 Months	**Burning throat**	**Cough**	**Nausea**	**Headache**	**Insomnia**	**Stomachache**	**Confusion**	**Dyspnea**

1 Month								
Arm 1 (E-Cigarette and Support)	22.9%	11.4%	4.3%	4.3%	1.4%	2.9%	1.4%	-
Arm 2 (Placebo)	4.3%	10%	5.7%	1.4%	1.4%	-	-	1.4%
3 Month								
Arm 1 (E-Cigarette and Support)	5.7%	10%	1.4%	-	1.4%	-	1.4%	-
Arm 2 (Placebo)	2.9%	2.9%	2.9%	-	-	-	-	1.4%

515 **Figure 1** CONSORT diagram for reporting trials1 [21]



516