General Hospital Psychiatry 93 (2025) 67–72

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: www.elsevier.com/locate/genhospsych

Effect of e-cigarettes for smoking cessation on depressive and anxiety symptoms: Secondary analysis of a randomized controlled trial☆

Anna Rihs[a,b], Anna Schoeni[a], Tamara Scharf[a,c], Julian Jakob[a,c,d], Kali Tal[a], Isabelle Jacot-Sadowski[e], Jean-Paul Humair[f], Anja Frei[g], Martin Brutsche[h], Nicolas Rodondi[a,b], Reto Auer[a,e], Stéphanie Baggio[a,i,*]

[a] Institute of Primary Health Care (BIHAM), University of Bern, Switzerland
[b] Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland
[c] Graduate School of Health sciences, University Bern, Switzerland
[d] Department of Paediatrics, Inselspital, Bern University Hospital, University of Bern, Switzerland
[e] Centre for Primary Care and Public Health (Unisanté), University of Lausanne, Switzerland
[f] Department of Primary Care Medicine, University Hospitals of Geneva, Switzerland
[g] Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Switzerland
[h] Lung Center, Kantonsspital St. Gallen, St. Gallen, Switzerland
[i] Laboratory of Population Health (#PopHealthLab), University of Fribourg, Fribourg, Switzerland

ARTICLE INFO

Keywords:
E-cigarettes
Electronic nicotine delivery systems (ENDS)
Depression
Anxiety
Mental health symptoms

ABSTRACT

Objective: This study aims to assess differences in depressive and anxiety symptoms at 6-month follow-up in a smoking cessation trial using e-cigarettes as quitting aids.
Methods: We conducted a secondary analysis of the Swiss multicentre ESTxENDS smoking cessation randomized controlled trial (RCT) assessing differences in depressive (Patient Health Questionnaire-9, PHQ-9, range: 0–27) and anxiety symptoms (General Anxiety Disorder-7, GAD-7, range: 0–21) at 6-month follow-up comparing participants who received e-cigarettes to those who received smoking cessation counseling alone.
Results: Of 1244 participants 913 completed the PHQ-9 and 884 the GAD-7 at 6-month follow-up. Mean PHQ-9 scores (SD) at 6 months for the intervention group were 3.7 (3.9), control group: 4.0 (4.2); mean GAD-7 scores (SD) at 6 months for the intervention group were 4.6 (4.3), control group: 4.6 (4.4). Multivariable analyses showed no evidence of a clinically relevant intervention effect on the PHQ-9 [coefficient − 0.101, 95 % CI -0.182 to −0.019, $p = .016$, corresponding to a 0.9 decrease of the original PHQ-9 score] and the GAD-7 scores [coefficient − 0.056, 95 % CI -0.135 to 0.022, $p = .160$] in the main adjusted models.
Conclusions: Among smokers who participated in the ESTxENDS smoking cessation trial, we found distribution of e-cigarettes for smoking cessation in addition to standard counseling compared to counseling alone had no clinically relevant effect on depressive or anxiety symptoms at 6-month follow-up.
Trial Registration: ClinicalTrials NCT03603340

1. Introduction

E-cigarettes (electronic nicotine delivery systems or ENDS) are increasingly popular among smokers who want to quit and may be efficacious smoking cessation aids [1]. However we do not know if they can be safely used by smokers with regards to mental health symptoms. People with mental illnesses are more likely to smoke, start smoking earlier, and smoke more heavily than those in the general population [2]. Depression is twice as common among smokers than non-smokers [3] and people with depression who try to quit smoking are less likely to succeed than those without depression [4,5]. Mental health professionals may fear that patients' depressive symptoms will worsen after quitting [6] and hesitate to encourage smokers with depression to quit. Clinicians may be discouraged from recommending e-cigarettes for

☆ Funding: Swiss National Science Foundation via the "Investigator-initiated clinical trials – IICT" grant # 173552, Swiss Tobacco Prevention Fund (TPF) #19.017477, Swiss Cancer Research (SCR) #KFS4744-02-2019 and LungeZürich.
* Corresponding author at: Institute of Primary Health Care (BIHAM), University of Bern, Mittelstrasse 43, CH-3012 Bern, Switzerland.
E-mail address: stephanie.baggio@unibe.ch (S. Baggio).

https://doi.org/10.1016/j.genhosppsych.2025.01.011
Received 9 July 2024; Received in revised form 14 January 2025; Accepted 14 January 2025
Available online 16 January 2025

smoking cessation to people with mental illness because there is little empirical evidence on the safety of e-cigarettes concerning mental health [7], and public health debates about the efficacy and safety of e-cigarettes in this population, e.g., in Australia [8,9], are ongoing.

Clinicians need to know if using e-cigarettes for smoking cessation influences depressive and anxiety symptoms. A recent Cochrane review of 102 smoking cessation studies about mental health after quitting did not consider e-cigarettes as smoking cessation aid but concluded that smoking cessation does not change and may improve smokers' mental health after smoking cessation [10]. This review included a heterogenous selection of mostly secondary analyses from randomized controlled trials (RCTs) and longitudinal studies, some of which found that depressive symptoms improved more in abstainers than in continuing smokers [11–15]. Other studies, including the largest smoking cessation RCT, showed similar improvement of depressive symptoms, independent of smoking status [5,16,17]. Data from cross-sectional and longitudinal observational studies on e-cigarettes and mental health suggested a relationship between worse mental health and use of e-cigarettes but were not designed to establish causality [18–23], so there is pressing need to investigate the effect of e-cigarettes on mental health symptoms within an RCT.

The large Efficacy, Safety and Toxicology of Electronic Nicotine Delivery Systems as an aid for smoking cessation (ESTxENDS) RCT offered the opportunity to compare the effect of e-cigarettes and standard of care smoking cessation counseling on depressive and anxiety symptoms to that of standard counseling alone in a self-selected sample of individuals willing to quit smoking from the general population. Six months after target quit date, we averaged and compared scores for depression and anxiety symptoms in the intervention and control group, and also compared the change in scores between baseline and 6 months. An exploratory per-exposure analysis determined potential associations between smoking, e-cigarette use and depressive or anxiety symptoms.

2. Methods

2.1. Study design and participants

This study is a secondary analysis of the ESTxENDS trial. ESTxENDS, an open-label, multicenter RCT conducted in Switzerland (described in detail elsewhere [24]), tested the effect of supplementing standard of care counseling with free e-cigarettes and e-liquids for 6 months, and compared the outcomes to standard counseling alone. Participants were recruited via advertisements on social media, in the lay press, in health care facilities and on public transport. Inclusion criteria were adults (≥18 years) smoking at least 5 cigarettes per day in the last 12 months and willing to quit smoking within the next 3 months. Exclusion criteria were minimal: being pregnant or breast-feeding and use of nicotine replacement therapy, e-cigarettes or tobacco heating systems in the previous 3 months. Psychiatric comorbidities were not exclusion criteria. The local ethics committees of each participating study site approved the trial. Participants were randomized in a centralized computed process (ratio 1:1). For this study, we used data from the baseline visit and the follow-up visit that took place 6 months after the smoker's target quit date.

2.2. Intervention

The intervention group participants received 2 e-cigarette devices and e-liquids with or without nicotine for free, which they could consume ad libitum for 6 months, they also received standard of care smoking cessation counseling. The control group participants received only standard counseling. Smoking cessation counseling was provided in person at the first clinical visit, over the phone at target quit date, one week later, and again at weeks 2, 4, and 8 after target quit date. After 6 months, participants were invited to visit the clinic in person.

2.3. Measures

Depression. We used the Patient Health Questionnaire-9 items (PHQ-9) to assess self-reported depressive symptoms and their severity in the 2-week period prior to baseline and 6-month follow-up. The PHQ-9 is a validated questionnaire based on the DSM-IV's diagnostic criteria for major depression and is sensitive to change over time [25]. It is also a preferred measure for assessing the severity of depression according to the DSM-5 [26]. Total score indicates the severity of suspected depression (range: 0–27, higher values indicate worse symptoms). The internal consistency was excellent at baseline and 6 months (Cronbach alpha = 0.81 at baseline and 0.82 at 6 months). For the subgroup analysis, we used the recommended cut-off of 9 (moderate depression) [27].

Anxiety. Symptoms of generalized anxiety disorder (GAD) were assessed with the validated GAD-7 item questionnaire in the 2-week period prior to baseline and 6-month follow-up [28]. The DSM-IV's diagnostic criteria were used to validate the GAD-7, and it is a useful tool to assess the severity of DSM-5 GAD [29]. Total score indicates severity of anxiety symptoms (range: 0–21, higher values indicate worse symptoms). The internal consistency was excellent at baseline and 6 months (Cronbach alpha = 0.89 at both time points). For the subgroup analysis, we used the recommended cut-off of 9 (moderate anxiety) [27].

Smoking characteristics. Participants took the Fagerström Test for Cigarette Dependence (range 1–10, higher scores indicate greater dependency) [30]. We assessed the number of cigarettes smoked each day and the number of earlier quit attempts.

Smoking status at 6-month follow-up. In ESTxENDS, a range of smoking cessation outcomes were assessed at the 6-month follow-up visit. In this analysis, we used 7-day point-prevalence abstinence, computed based on self-reported use of any tobacco cigarettes or e-cigarettes for the 7 days before the 6-month visit. For our per-exposure analysis, we divided participants into 2 groups: e-cigarette use (yes/no) and tobacco smoking (yes/no).

Baseline sociodemographic and health variables. We assessed gender, Body Mass Index (BMI), education level, working situation and antidepressant and anxiolytic (benzodiazepines, hypnotics, or sedatives) use. To define the medication, we adhered to the standard set by the WHO Collaborating Centre for Drug Statistics Methodology. Participants completed the Alcohol Use Disorders Identification Test-Concise (AUDIT-C), which assessed frequency and quantity of alcohol consumption and the number of times per year participants consumed 6 or more standard drinks on the same day. We used the usual cut-off score of ≥3 points for women and ≥ 4 points for men to indicate potential problematic alcohol use [31]. Participants were asked if they used cannabis during the last 6 months.

2.4. Statistics

Sample size was computed for the primary ESTxENDS outcome (smoking cessation at 6-month follow-up, Trial Registration: ClinicalTrials NCT03589989, [24]). We did not compute sample size for this secondary analysis. We made a separate entry for secondary analyses on clinicaltrials.gov, so we could formulate the main outcome for secondary analyses a priori (Trial Registration: ClinicalTrials NCT03603340).

We first used descriptive statistics to summarize baseline characteristics as percentages and n or means with standard deviations. We explored patterns of missing values and used multiple imputation. A few baseline characteristics were imputed for participants who took the PHQ-9 and GAD-7 at 6 months (4 values for the BMI, 1 for the PHQ-9, 2 for the GAD-7, and 7 for the AUDIT-C score), as well as missing PHQ-9 and GAD-7 scores at 6 months. We used multiple imputation by chained equation, with m = 10 and use of logit regression for binary variables with missing values and truncated regression with limits using the minimum and maximum values observed in the sample for continuous variables. Predictors were sex, age, level of education, work status, cannabis consumption during the last 6 months, number of previous quit

attempts, Fagerström score, number of cigarettes smoked daily, antidepressant and anxiolytic use. All analyses were performed on the imputed datasets. We next used linear regression models to compare groups (intervention vs. control), first for depressive, then for anxiety symptoms. Adjusted models controlled for baseline variables (baseline levels of depressive and anxiety symptoms, Fagerström score, number of cigarettes smoked daily, number of previous quit attempts, problematic alcohol use (vs. not problematic & none), cannabis consumption during the last 6 months, gender, BMI, education level, working situation, antidepressant and anxiolytic use). Before interpreting the adjusted models, we checked for multicollinearity and removed multicollinear variables. We conducted intention-to-treat analyses according to baseline randomization. Additionally, we performed a subgroup analysis on 1) participants with a baseline PHQ-9 score above 9 and 2) participants with a baseline GAD-7 score above 9. We used similar analyses as described above. For our per-exposure analysis, we used 7-day point-prevalence data collected at the 6-month visit to classify participants into 2 groups [32]. Our linear regression models tested the association of exposure to tobacco smoking, e-cigarette use, and their interaction with 1) depressive and 2) anxiety symptoms. We present unadjusted and adjusted models. Since using adjusted models improves precision and power, we considered them our primary analyses in this study [33]. We present additional unadjusted and adjusted models of the change in PHQ-9 and GAD-7 from baseline to the 6-month follow-up visit, as described for the main outcome. For all models, we report a measure of effect size (adjusted R^2). When associations between the group and the outcomes were statistically significant, we converted them in the original scale for interpretability of clinical relevance. All analyses were conducted in STATA, version 18, with a two-tailed 0.05 significance level.

3. Results

3.1. Baseline characteristics

A total of 2027 smokers were screened (399 did not meet inclusion criteria, 382 declined participation); 1246 were randomized (622 in the intervention group, 624 in the control group); and 2 participants (1 per group) were excluded in this analysis because no PHQ-9/GAD-7 data was available both at baseline and 6 months. We included 1244 participants (621 in the intervention; 623 in the control group); mean (SD) age was 41.1 (13.5) years; 47 % were women (Table 1). Participants were recruited between July 2018 and June 2021. Data of the 6 months visits were collected until March 2022. A total of 913 participants (504 in the intervention; 409 in the control group; Supplement eTable 1) completed the PHQ-9 at the 6-month follow-up visit. Mean PHQ-9 scores and standard deviations (SD) at baseline were 4.4 (4.2) in the intervention group and 4.4 (4.3) in the control group. A total of 884 participants completed the GAD-7 at 6 months follow-up; mean GAD-7 scores at baseline were 5.5 (4.4) in the intervention group and 5.3 (4.6) in the control group. Approximately 12 % of participants were taking antidepressants at baseline; 3 % were taking anxiolytics. About 33 % of participants had consumed cannabis during the last 6 months; 61 % had potentially problematic alcohol use.

3.2. Intention-to-treat analyses

Mean (SD) PHQ-9 score at 6 months in the intervention group was 3.7 (3.9) and 4.0 (4.2) in the control group (Table 2). We found no evidence the intervention influenced the PHQ-9 score in the unadjusted analysis [coefficient − 0.084, 95 % CI -0.181 to 0.013, $p = .091$, effect size 0.2 %] (Table 3). In the main adjusted model, we found a statistically significant difference [coefficient − 0.101, 95 % CI -0.182 to -0.019, $p = .016$, effect size 32.8 %] corresponding to a 0.9 decrease of the original PHQ-9 score in the intervention group compared to the control group (Table 3). Mean (SD) difference in PHQ-9 score from baseline to 6 months was − 0.5 (3.6) in the intervention group and − 0.2 (3.7) in the control group. No model showed the intervention influenced the change in PHQ-9 score [unadjusted analysis: coefficient − 0.385, 95 % CI -0.844 to 0.074, $p = .099$, effect size 0.2 %; main adjusted model: coefficient − 0.330, 95 % CI -0.743 to 0.083, $p = .116$, effect size 22.5

Table 1
Baseline characteristics.

Characteristic	Total Participants	Control Group	Intervention Group	Imputed Values
Participants (N)	1244	623	621	
Women - no. (%)	585 (47.0)	295 (47.4)	290 (46.7)	0
BMI - kg/m^2	25.7 (4.9, 15.2;49.9)	25.7 (4.9, 15.2;49.9)	25.6 (4.9, 15.7;44.5)	4
Age - years	41.1 (13.5,18;79)	41.7 (13.3,18;78)	40.4 (13.6,18;79)	0
Education level categorized - no. (%)				0
Obligatory school I/Other/None	95 (7.6)	45 (7.2)	50 (8.1)	
Secondary education II	568 (45.7)	277 (44.5)	291 (46.9)	
Tertiary education III	581 (46.7)	301 (48.3)	280 (45.1)	
Work situation categorized - no. (%)				0
Unemployed	237 (19.1)	111 (17.8)	126 (20.3)	
Employed/self-employed/In education	1007 (81.0)	512 (82.2)	495 (79.7)	
Smoking characteristics				
Fagerström score	4.3 (2.3, 0;10)	4.4 (2.3, 0;10)	4.3 (2.3, 0;10)	0
Numbers of cigarettes smoked daily	16.8 (7.7, 5;60)	16.9 (7.5, 5;50)	16.8 (7.8, 5;60)	0
Participants with at least one previous quit attempt - no. (%)	1061 (85.3)	530 (85.1)	531 (85.5)	0
Number of previous quit attempts	2.5 (3.7, 0;50)	2.5 (3.8, 0;50)	2.4 (3.6, 0;50)	0
Psychiatric characteristics				
PHQ-9 score at baseline	4.4 (4.2, 0;25)	4.3 (4.2, 0;25)	4.4 (4.2, 0;25)	1
Participants with PHQ-9 score at baseline>9 - no. (%)	155 (12.5)	73 (11.7)	82 (13.2)	1
GAD-7 score at baseline	5.4 (4.5, 0;21)	5.3 (4.6, 0;21)	5.5 (4.4, 0;21)	2
Participants with GAD-7 score at baseline>9 - no. (%)	215 (17.3)	102 (16.4)	113 (18.2)	2
Antidepressants at baseline no. (%)	151 (12.1)	79 (12.7)	72 (11.6)	0
Anxiolytics at baseline no. (%)	42 (3.4)	19 (3.1)	23 (3.7)	0
Alcohol use - AUDIT-C score ≥ 3 women/≥4 men) - no. (%)	752 (60.8)	387 (62.8)	365 (58.8)	7
Cannabis use last 6 months – no. (%)	416 (33.4)	196 (31.5)	220 (35.4)	0

Means (SD, ranges) are reported unless otherwise stated. SD = Standard Deviation, PHQ-9 = Patient Health Questionnaire-9 items (range: 0–27), GAD-7 = General Anxiety Disorder-7 (range: 0–21), AUDIT-C = Alcohol Use Disorders Identification Test-Concise. All analyses used multiple imputation by chained equation for missing values.

Table 2
Depressive and anxiety symptoms at 6 months.

Outcome	Control Group	Intervention Group
Mean PHQ-9 score (SD, range)	4.0 (4.2,0–22)	3.7 (3.9,0;22)
Mean change in PHQ-9 score from BL to M6 (SD, range)	-0.2 (3.7, −14;19)	−0.5 (3.6, −17;15)
Mean GAD-7 score (SD, range)	4.6 (4.4, 0;21)	4.6 (4.3,0;21)
Mean change in GAD-7 score from BL to M6 (SD, range)	−0.6 (3.9, −15;13)	−0.6 (3.8, −13;17)

SD = Standard Deviation, PHQ-9 = Patient Health Questionnaire-9 items (range: 0–27), GAD-7 = General Anxiety Disorder-7 (range: 0–21).
All analyses used multiple imputation by chained equation for missing values.

Table 3
Unadjusted and adjusted linear regressions for depressive and anxiety symptoms outcome at 6 months.

	Unadjusted models			Adjusted models[1]		
Outcome	Coefficient (95 % CI)	p-value	Effect size	Coefficient (95 % CI)	p-value	Effect size
PHQ-9 score	−0.084 (−0.181 to 0.013)	0.091	0.2 %	−0.101 (−0.182 to −0.019)	0.016	32.8 %
Change in PHQ-9 score	−0.385 (−0.844 to 0.074)	0.099	0.2 %	−0.330 (−0.743 to 0.083)	0.116	22.5 %
GAD-7 score	−0.030 (−0.125 to 0.065)	0.536	0.0 %	−0.056 (−0.135 to 0.022)	0.160	34.2 %
Change in GAD-7 score	−0.256 (−0.720 to 0.207)	0.277	0.0 %	0.094 (−0.513 to 0.325)	0.659	20.7 %

CI = Confidence Interval, PHQ-9 = Patient Health Questionnaire-9 items (range: 0–27), GAD-7 = General Anxiety Disorder-7 (range: 0–21).
All analyses used multiple imputation by chained equation for missing values. The coefficient is a slope, which corresponds to the difference between the standard counseling (reference) and e-cigarettes + standard counseling groups.
[1] The adjusted model controlled for baseline levels of depressive and anxiety symptoms, smoking characteristics (Fagerström, number of cigarettes smoked daily, number of previous quit attempts), problematic alcohol use, cannabis use last 6 months, gender, BMI, education level, working situation, antidepressant and anxiolytics use at baseline.

%].

Mean (SD) GAD-7 scores at 6 months were 4.6 (4.3) in the intervention group and 4.6 (4.4) in the control group (Table 2). We found no evidence the intervention influenced the GAD-7 score in the unadjusted model [coefficient − 0.030, 95 % CI -0.125 to 0.065, $p = .536$, effect size 0.0 %], in the main adjusted model [coefficient − 0.056, 95 % CI -0.135 to 0.022, $p = .160$, effect size 34.2 %], or in any other model (Table 3). Mean (SD) difference in GAD-7 score from baseline to 6 months was − 0.6 (3.8) in the intervention group and − 0.6 (3.9) in the control group. We found no evidence the intervention influenced the change in GAD-7 score [unadjusted analysis: coefficient − 0.256, 95 % CI: -0.720 to 0.207, $p = .277$, effect size 0.0 %; main adjusted model: coefficient 0.094, 95 % CI -0.513 to 0.325, $p = .659$, effect size 20.7 %].

A subgroup analysis including participants with a baseline PHQ-9 score above 9 (intervention group $N = 55$, control group $N = 42$, baseline antidepressant use: 27 %, baseline anxiolytic use: 6 %) showed overall high mean (SD) PHQ-9 scores with 8.7 (5.0) in the intervention group and 9.8 (5.6) in the control group at 6 months (Supplement eTable 2a). No model showed the intervention influenced the mean PHQ-9 score in this subgroup [unadjusted analysis: coefficient − 0.093, 95 % CI -0.352 to 0.166, $p = .478$, effect size 0.5 %; main adjusted model: coefficient − 0.102, 95 % CI -0.359 to 0.156, $p = .433$, effect size 21.2 %], or in any other model (Supplement eTable 3a). Mean (SD) differences in PHQ-9 scores from baseline to 6 months were − 3.8 (5.4) in the intervention group and − 3.4 (4.8) in the control group. No model showed the intervention influenced the change in PHQ-9 score [unadjusted analysis: coefficient − 0.437, 95 % CI -2.518 to 1.644, $p = .677$, effect size 0.9 %; main adjusted model: coefficient − 1.038, 95 % CI -3.145 to 1.070, $p = .330$, effect size 18.0 %].

A subgroup analysis including participants with a baseline GAD-7 score above 9 (intervention group $N = 80$, control group $N = 65$, baseline antidepressant use: 21 %, baseline anxiolytic use: 7 %) showed overall high mean (SD) GAD-7 scores with 9.2 (5.1) in the intervention group and 9.4 (5.8) in the control group at 6 months (Supplement eTable 2b). We found no evidence the intervention influenced the GAD-7 score in this subgroup in the unadjusted model [coefficient − 0.027, 95 % CI -0.195 to 0.249, $p = .809$, effect size 0.6 %], in the main adjusted model [coefficient 0.101, 95 % CI -0.122 to 0.324, $p = .371$, effect size 16.2 %], or in any another model (Supplement eTable 3b). Mean (SD) differences in GAD-7 scores from baseline to 6 months were − 3.5 (4.9) in the intervention group and − 4.1 (5.4) in the control group. We found no evidence the intervention influenced the change in GAD-7 score [unadjusted analysis: coefficient 0.458, 95 % CI: -1.237 to 2.153, $p = .594$, effect size 0.5 %; main adjusted model: coefficient 0.186, 95 % CI -1.581 to 2.949, $p = .837$, effect size 9.4 %].

3.3. Per-exposure analyses

A total of 1056 participants completed the 7-day-point prevalence question concerning tobacco smoking and e-cigarette use, 399 used e-cigarettes and 533 smoked tobacco. The simple linear regression showed no evidence using e-cigarettes or smoking tobacco influenced the PHQ-9 score in the unadjusted model (Table 4a). In the main adjusted model, the use of e-cigarettes showed a statistically significant difference [coefficient − 0.141, 95 % CI −0.261 to −0.022, $p = .020$, effect size 35.5 %] corresponding to a 0.9 decrease of the original PHQ-9 score in e-cigarette users compared to non-users. The simple linear regression showed no evidence using e-cigarettes or smoking tobacco influenced the GAD-7 score in the unadjusted analysis or in the main adjusted model (Table 4b).

4. Discussion

Among smokers who participated in the ESTxENDS smoking cessation trial, we found distribution of e-cigarettes for smoking cessation in addition to standard counseling compared to counseling alone had no clinically relevant effect on depressive or anxiety symptoms at 6-month follow-up. The results from the adjusted analysis concerning the depressive symptoms at 6 months were statistically significant

Table 4a
Per-exposure analysis: Linear regressions of depressive symptoms at 6 months according to exposition to e-cigarette use and tobacco smoking.

Groups	Unadjusted models			Adjusted models[1]		
	Coefficient (95 % CI)	p-value	Effect size	Coefficient (95 % CI)	p-value	Effect size
E-cigarette users	−0.091 (−0.235 to 0.054)	0.220	0.2 %	−0.141 (−0.261 to −0.022)	0.020	35.5 %
Cigarette smokers	0.130 (−0.052 to 0.313)	0.162	0.2 %	0.048 (−0.102 to 0.198)	0.529	35.5 %
Interaction between *E*-cigarette users and cigarette smokers	−0.084 (−0.310 to 0.143)	0.469	0.2 %	−0.099 (−0.286 to 0.087)	0.295	35.5 %

Table 4b
Per-exposure analysis: Linear regressions of anxiety symptoms at 6 months according to exposition to e-cigarette use and tobacco smoking.

Groups	Unadjusted models			Adjusted models[1]		
	Coefficient (95 % CI)	p-value	Effect size	Coefficient (95 % CI)	p-value	Effect size
E-cigarette users	−0.000 (−0.147 to 0.147)	0.997	0.0 %	0.007 (−0.131 to 0.116)	0.908	35.8 %
Cigarette smokers	0.007 (−0.178 to 0.192)	0.940	0.0 %	0.058 (−0.211 to 0.100)	0.480	35.8 %
Interaction between E-cigarette users and cigarette smokers	0.094 (−0.134 to 0.322)	0.419	0.0 %	0.093 (−0.098 to 0.283)	0.339	35.8 %

CI = Confidence Interval, PHQ-9 = Patient Health Questionnaire-9 items (range: 0–27), GAD-7 = General Anxiety Disorder-7 (range: 0–21).
All analyses used multiple imputation by chained equation for missing values. The coefficient is a slope, which corresponds to the difference between the standard counseling (reference) and e-cigarettes + standard counseling groups.
[1] The adjusted model controlled for baseline levels of depressive and anxiety symptoms, smoking characteristics (Fagerström, number of cigarettes smoked daily, number of previous quit attempts), problematic alcohol use, cannabis use last 6 months, gender, BMI, education level, working situation, antidepressant and anxiolytics use at baseline.

underlined by the slightly lower PHQ-9 score in the intervention group at 6 months. However, this effect was clinically not relevant due to the very small difference (0.9 difference in the original PHQ-9 score ranging from 0 to 27). A clinically relevant difference with regards to the PHQ-9 score would be 5 points [34]. The results were non-significant in two subgroup analyses of participants with elevated depressive or anxiety scores at baseline. This underlines that distribution of e-cigarettes for smoking cessation had no clinically relevant effect on depressive or anxiety symptoms at 6-month follow-up not only in the whole study population, but also in the subgroups with mental health symptoms at baseline. In the per-exposure analysis depressive and anxiety symptoms in tobacco smokers were not significantly different from those of non-smokers at 6 months. Anxiety symptoms in e-cigarette users were not significantly different from those of non-users at 6 months. The adjusted per-exposure analysis on depressive symptoms of e-cigarette users compared to non-users at 6 months showed a statistically significant difference [coefficient − 0.141, 95 % CI -0.261 to −0.022, $p = .020$, effect size 35.5 %]. However, this effect was clinically not relevant due to the very small difference, as it corresponds to a 0.9 difference in the original PHQ-9 score ranging from 0 to 27. The interaction between tobacco smoking and e-cigarette use was not statistically significant.

In ESTxENDS, 7-day self-reported smoking abstinence was 53.4 % in the intervention group and 21.1 % in the control group [24]. Smoking abstinence rate was higher in the intervention group at 6 months, depression scores improved similarly across groups. Our results align with those of an RCT that compared the neuropsychiatric safety of varenicline, bupropion and nicotine patches among smokers with and without psychiatric comorbidities: depression scores over all treatment groups improved similarly [5]. Our findings also accord with those of a recent Cochrane review of 102 studies about smoking cessation (not including e-cigarettes) and mental health outcomes, suggesting that smoking cessation does not worsen mental health [10].

Our results show that participants who received e-cigarettes for smoking cessation along with SOC did not have more depressive or anxiety symptoms than participants who received SOC alone. Previous observational studies reported a higher proportion of e-cigarette use among people with mental health problems [18–23]. Similar associations have been described in the past, before e-cigarettes were available for tobacco smoking [2]. In a longitudinal analysis of observational data e-cigarette use did not predict subsequent depression, but depression predicted subsequent use of e-cigarettes [22]. This would suggest that e-cigarette use is a consequence of depression and not the reverse. Our findings allow to explore these associations further and show that e-cigarettes for smoking cessation do not lead to worse mental health symptoms. Our results can't however be extrapolated to persons who use e-cigarettes for other purposes than for smoking cessation. Concerning our results there are at least two possible interpretations from our point of view. First, if smoking cessation has a positive effect on mental health and if e-cigarettes have a negative effect on mental health, the effects might have canceled each other out in this study. Second, it is also imaginable that neither the use of e-cigarettes nor smoking cessation has a relevant effect on mental health and the improvement is just a spontaneous decrease of depressive and anxiety symptoms over 6 months.

4.1. Limitations

Our study had seven limitations. First, the attrition rate was high at 6 months (27 % for the PHQ-9; 29 % for the GAD-7) and was higher in the control group than in the intervention group. We accounted for attrition using multiple imputation by chained equation, assuming that data were missing at random. While this approach helps mitigate bias, we acknowledge that if important unmeasured variables related to missingness were not included in our imputation model, some selection bias may remain. Additionally, 2 participants were excluded in this analysis because they dropped out very early and had missing values for most variables that were used in our adjusted model. Second, depression and anxiety questionnaires were collected at only 2 time points (baseline and 6-month follow-up visit); the calculated change score does not imply a linear progression, it is possible that during the 6 months there were other oscillations of the mental health symptoms. Third, the ESTxENDS trial was a trial that offered e-cigarettes and e-liquids for smoking cessation to the intervention group but participants were under no obligation to use them and we did not quantify ENDS use at 6-month follow-up. Our results cannot be generalized to people who use e-cigarettes for reasons other than smoking cessation. Fourth, psychiatric comorbidities were not systematically assessed in this study but data on baseline antidepressant and anxiolytic medication was collected and could be used to identify participants with depression or anxiety requiring pharmacological treatment at baseline. Fifth, we did not analyze psychiatric medication use at 6-month follow-up or changes in such medication use. Sixth, we did not ask participants whether they were involved in psychotherapy or other treatments for mental health symptoms which could explain improvement of depressive and anxiety symptoms. Seventh, as the ESTxENDS trial was not powered to detect an effect in a psychiatric population, these results need to be interpreted cautiously. Future research should define the needed sample size of participants with mental health problems a priori and test if mental health safety of e-cigarettes can be confirmed.

The mechanisms of interaction between depression, anxiety, smoking cessation, and e-cigarettes have yet to be fully elucidated. Researchers who conduct studies to test the efficacy and safety of e-cigarettes should systematically assess psychiatric comorbidities and stratify participants in two groups considering psychiatric disorders.

5. Conclusion

Distribution of e-cigarettes for smoking cessation had no significant effect on depressive and anxiety symptoms at 6-month follow-up of the ESTxENDS smoking cessation trial in a self-selected sample of individuals willing to quit smoking from the general population. Clinicians considering adding e-cigarettes to standard of care smoking cessation counseling can be reassured that on average, changes in depressive and anxiety symptoms after 6 months are unlikely due to adding e-cigarettes to standard smoking cessation counseling.

Author statement

Role of the Funding Source.

The funding bodies had no role in the trial design; the collection, monitoring, analysis, or interpretation of the data; or the writing of the manuscript.

CRediT authorship contribution statement

Anna Rihs: Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Anna Schoeni:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Tamara Scharf:** Writing – review & editing, Conceptualization. **Julian Jakob:** Writing – review & editing, Conceptualization. **Kali Tal:** Writing – review & editing, Conceptualization. **Isabelle Jacot-Sadowski:** Writing – review & editing, Investigation, Conceptualization. **Jean-Paul Humair:** Writing – review & editing, Investigation, Conceptualization. **Anja Frei:** Writing – review & editing, Investigation, Conceptualization. **Martin Brutsche:** Writing – review & editing, Investigation, Conceptualization. **Nicolas Rodondi:** Writing – review & editing, Investigation, Conceptualization. **Reto Auer:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Stéphanie Baggio:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors have no conflict of interest except for Martin Brutsche. Martin Brutsche has the following interests:

- AstraZeneca Schweiz: invited to scientific talks
- GlaxoSmithKline: consultant in scientific advisory board
- Merck Sharp and Dohme: consultant in scientific advisory board
- Novartis Pharma AG: consulting in the field of sarcoidosis

Acknowledgements

We thank all trial participants, the staff at the clinical trial unit of the University of Bern and the trial nurses at each site.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2025.01.011.

Data availability

Data will be made available on request.

References

[1] Lindson N, Butler AR, McRobbie H, Bullen C, Hajek P, Begh R, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev 2024;(1):1–342.
[2] Fluharty M, Taylor AE, Grabski M, Munafò MR. The Association of Cigarette Smoking with Depression and Anxiety: a systematic review. Nicotine Tob Res 2017;19:3–13.
[3] Weinberger AH, Gbedemah M, Wall MM, Hasin DS, Zvolensky MJ, Chaiton M, et al. Depression among non-daily smokers compared to daily smokers and never-smokers in the United States: an emerging problem. Nicotine & tobacco research : Off J Soc ResNicotine Tobacco 2017;19:1062–72.
[4] Cook BL, Wayne GF, Kafali EN, Liu Z, Shu C, Flores M. Trends in smoking among adults with mental illness and association between mental health treatment and smoking cessation. Jama 2014;311:172–82.
[5] Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet 2016;387:2507–20.
[6] Sheals K, Tombor I, McNeill A, Shahab L. A mixed-method systematic review and meta-analysis of mental health professionals' attitudes toward smoking and smoking cessation among people with mental illnesses. Addiction 2016;111:1536–53.
[7] Gentry S, Forouhi NG, Notley C. Are electronic cigarettes an effective aid to smoking cessation or reduction among vulnerable groups? A systematic review of quantitative and qualitative evidence. Nicotine Tob Res 2018;21:602–16.
[8] Scott JG, Jhetam S, Chen R, Daglish M. Should psychiatrists support the availability of nicotine e-cigarettes in Australia? Australas Psychiatry 2019;27:392–5.
[9] McKeon G, Scott JG. Smoke and mirrors: support from psychiatrists for nicotine e-cigarette availability in Australia. Austral & New Zealand J Psychiatr 2023;57:169–80.
[10] Taylor GM, Lindson N, Farley A, Leinberger-Jabari A, Sawyer K, Te Water Naude R, et al. Smoking cessation for improving mental health. Cochrane Database Syst Rev 2021;3:CD013522.
[11] Covey LS, Hu M-C, Winhusen T, Lima J, Berlin I, Nunes E. Anxiety and depressed mood decline following smoking abstinence in adult smokers with attention deficit hyperactivity disorder. J Subst Abuse Treat 2015;59:104–8.
[12] Lechner WV, Sidhu NK, Cioe PA, Kahler CW. Effects of time-varying changes in tobacco and alcohol use on depressive symptoms following pharmaco-behavioral treatment for smoking and heavy drinking. Drug Alcohol Depend 2019;194:173–7.
[13] Lee EJ. Long-term effects of smoking cessation on depressive symptoms, resilience, coping skills, and serotonin. Psychiat Quarte 2020;91:263–71.
[14] Levy DE, Chang Y, Regan S, Tindle HA, Singer DE, Rigotti NA. Improvements in health-related quality of life among smokers who quit after hospitalization. Prev Med 2018;110:38–46.
[15] Secades-Villa R, González-Roz A, Vallejo-Seco G, Weidberg S, García-Pérez Á, Alonso-Pérez F. Additive effectiveness of contingency management on cognitive behavioural treatment for smokers with depression: six-month abstinence and depression outcomes. Drug Alcohol Depend 2019;204:107495.
[16] Schnoll RA, Hitsman B, Blazekovic S, Veluz-Wilkins A, Wileyto EP, Leone FT, et al. Longitudinal changes in smoking abstinence symptoms and alternative reinforcers predict long-term smoking cessation outcomes. Drug Alcohol Depend 2016;165:245–52.
[17] Prochaska JJ, Hall SM, Tsoh JY, Eisendrath S, Rossi JS, Redding CA, et al. Treating tobacco dependence in clinically depressed smokers: effect of smoking cessation on mental health functioning. Am J Public Health 2008;98:446–8.
[18] Pham T, Williams JVA, Bhattarai A, Dores AK, Isherwood LJ, Patten SB. Electronic cigarette use and mental health: a Canadian population-based study. J Affect Disord 2020;260:646–52.
[19] Saeed OB, Chavan B, Haile ZT. Association between E-cigarette use and depression in US adults. J Addict Med 2020;14:393–400.
[20] Becker TD, Arnold MK, Ro V, Martin L, Rice TR. Systematic review of electronic cigarette use (vaping) and mental health comorbidity among adolescents and young adults. Nicotine Tob Res 2020;23(3):415–25.
[21] Dawkins L, Ford A, Bauld L, Balaban S, Tyler A, Cox S. A cross sectional survey of smoking characteristics and quitting behaviour from a sample of homeless adults in Great Britain. Addict Behav 2019;95:35–40.
[22] Bandiera FC, Loukas A, Li X, Wilkinson AV, Perry CL. Depressive symptoms predict current E-cigarette use among college students in Texas. Nicotine Tob Res 2017;19:1102–6.
[23] Farrell KR, Karey E, Xu S, Gibbon G, Gordon T, Weitzman M. E-cigarette use, systemic inflammation, and depression. Int J Environ Res Public Health 2021;18.
[24] Auer R, Schoeni A, Humair J-P, Jacot-Sadowski I, Berlin I, Stuber MJ, et al. Electronic nicotine-delivery Systems for Smoking Cessation. N Engl J Med 2024;390:601–10.
[25] Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606–13.
[26] Zimmerman M. Symptom severity and guideline-based treatment recommendations for depressed patients: implications of DSM-5's potential recommendation of the PHQ-9 as the measure of choice for depression severity. Psychother Psychosom 2012;81:329–32.
[27] Kroenke K, Spitzer RL, Williams JB, Löwe B. The patient health questionnaire somatic, anxiety, and depressive symptom scales: a systematic review. Gen Hosp Psychiatry 2010;32:345–59.
[28] Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092–7.
[29] Diagnostic and statistical manual of mental disorders. DSM-5™. 5th ed. Arlington, VA, US: American Psychiatric Publishing, Inc.; 2013.
[30] 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;86:1119–27.
[31] Bradley KA, DeBenedetti AF, Volk RJ, Williams EC, Frank D, Kivlahan DR. AUDIT-C as a brief screen for alcohol misuse in primary care. Alcohol Clin Exp Res 2007;31:1208–17.
[32] Hughes JR, Carpenter MJ, Naud S. Do point prevalence and prolonged abstinence measures produce similar results in smoking cessation studies? A systematic review. Nicotine Tob Res 2010;12:756–62.
[33] Wang B, Susukida R, Mojtabai R, Amin-Esmaeili M, Rosenblum M. Model-robust inference for clinical trials that improve precision by stratified randomization and covariate adjustment. J Am Stat Assoc 2021:1–12.
[34] McMillan D, Gilbody S, Richards D. Defining successful treatment outcome in depression using the PHQ-9: a comparison of methods. J Affect Disord 2010;127:122–9.