Varenicline for smoking cessation in individuals who smoke cigarettes and use electronic cigarettes: a double-blind, randomised, placebo-controlled phase 3 trial

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Summary

Background The efficacy and safety of varenicline for smoking cessation among individuals who smoke tobacco cigarettes and also use electronic cigarettes (known e-cigarettes or vapes) have not been studied. We aimed to address this knowledge gap and examine predictors for smoking abstinence.

Methods In this double-blind, placebo-controlled, single-centre randomised trial in Italy, we enrolled adults who had used an e-cigarette daily for at least 12 months and who also smoked at least one tobacco cigarette per day and had a willingness to quit smoking. 155 participants were randomly assigned to receive either varenicline (n = 78) or matched placebo (n = 77). Varenicline (1 mg, administered twice daily for 12 weeks) was given in combination with smoking cessation counseling in dual users with an intention to quit smoking. Participants in both treatment groups received the same smoking cessation counselling throughout the whole duration of the study. The trial consisted of a 12-week treatment phase followed by a 12-week follow-up. The primary efficacy endpoint was continuous abstinence rate (CAR) in weeks 4–12. Secondary efficacy endpoints were the CAR in weeks 4–24 and 7-day point prevalence of smoking abstinence at weeks 12 and 24. This study is registered in EUDRACT, 2016-000339-42.

Findings Between November 2018, and February 2020, 114 participants (61 in the varenicline group and 53 in the placebo group) completed the intervention phase at week 12 and 88 participants (52 in the varenicline group and 36 in the placebo group) completed the follow-up phase at week 24. CARs were significantly higher for the varenicline vs placebo at each time-point: 50.0% vs 16.9% (OR = 4.9; 95% CI, 2.3–10.4; P < 0.0001) between weeks 4 and 12; and 48.7% vs 14.3% (OR = 5.7; 95% CI, 2.6–12.3; P < 0.0001) between weeks 4 and 24. The 7-day point prevalence of smoking abstinence was also higher for the varenicline than placebo at each time point. Adverse events were rated as mild or moderate and rarely led to treatment discontinuation.

Interpretation Our findings indicate that inclusion of varenicline in a cessation programme for adults who smoke and use e-cigarettes with an intention to quit smoking could result in smoking abstinence without serious adverse events. In the absence of evidence from other smoking cessation methods, it could be useful to suggest the use of varenicline in cessation programmes specifically designed to help dual users stop smoking. Further research in larger and more generalisable populations is required to strengthen such a suggestion.

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Research in context

Evidence before this study

Many individuals who use electronic cigarettes (known as e-cigarettes or vapes) with the intention of quitting traditional tobacco cigarette smoking continue to engage in both habits. In the USA, estimates suggest that a substantial proportion of adults, ranging from 40% to 60%, engage in dual use—i.e., simultaneously using both cigarettes and e-cigarettes. Despite a growing interest among health-care professionals and stake holders to help these dual users to quit smoking altogether, there is a current lack of concrete evidence to provide specific guidance for individuals who use both e-cigarettes and traditional cigarettes and who wish to stop smoking. There was a clear need for rigorous research to establish the effectiveness of interventions for dual users and to offer valuable insights for health authorities and health-care providers. Furthermore, limited information was available on the safety and efficacy of medications approved by the US Food and Drug Administration for smoking cessation in the context of individuals who both smoke traditional cigarettes and use e-cigarettes. This study was designed to address this critical knowledge gap by assessing the efficacy of varenicline in adult dual users.

Added value of this study

This double-blind, randomised, placebo-controlled trial is the first of its kind in that it aimed to examine the effectiveness of varenicline as a smoking cessation aid for adults who simultaneously smoke traditional cigarettes and use e-cigarettes. The findings of the study show the potential of varenicline in aiding these individuals in quitting smoking and achieving prolonged abstinence from tobacco cigarette use.

Implications of all the available evidence

The results of this trial could have substantial implications for the design of smoking cessation programmes for adults who engage in dual use of both e-cigarettes and traditional cigarettes and who are committed to quitting. The inclusion of varenicline in such smoking cessation programmes could be a viable strategy, given that our findings suggest that varenicline usage appears to be associated with prolonged abstinence without major adverse events. Moreover, this evidence has the potential to inform future recommendations made by health authorities and health-care providers, with the goal of addressing the widespread issue of dual use of cigarettes effectively.

Introduction

Vaping products are combustion-free nicotine delivery systems (i.e., electronic cigarettes; hereafter referred to as e-cigarettes) that have become popular among adult tobacco cigarette smokers, with the global number of e-cigarette users estimated at about 68 million in 2020.[1] Although e-cigarette users report buying them to quit traditional tobacco cigarette smoking,[2,3] many continue to smoke while vaping.[4,5] In the USA, the number of adults who currently both smoke traditional cigarettes and use e-cigarettes (i.e., dual users) is estimated at 40–60%.[4,5]

E-cigarettes may be effective in helping adult smokers to quit.[6–8] Also, a marked reduction in toxic chemicals and beneficial impact on health effect indicators have been shown in exclusive e-cigarette users compared to cigarette smokers.[9–11] However, the extent to which smoking-related harm is reduced when e-cigarettes are used concurrently with combustible cigarettes is less clear.[12–14] Further complicating the analysis, dual users are highly heterogeneous in their use of these products, with significant variability observed across population subgroups by age, race, socioeconomic, and psychosocial status.[15] Given these uncertainties, it is imperative that dual use patterns and health effects be thoroughly investigated.

In our experience and according to recent surveys, interest in stopping smoking altogether has grown among dual users, and particularly during the COVID-19 pandemic.[16–18] Dual users' desire to stop smoking altogether appears to be largely due to concern about the well-known health risks of cigarette smoking, the high cost of tobacco cigarettes, and the need to break away from dependency on tobacco cigarettes.[19] In spite of the growing interest in smoking cessation among dual users, there is little evidence to inform specific recommendations for people who vape and smoke and intend to stop smoking. Although guidelines on best management for smoking cessation are available,[20,21] there are no specific evidence-based recommendations for individuals who smoke cigarettes and use e-cigarettes and intend to quit cigarette smoking.[22] Rigorous research is

required to establish effectiveness of interventions for e-cigarette and dual use cessation among specific subpopulations and to guide the decisions of health authorities and healthcare providers. In particular, there is limited information about the efficacy and safety of medications approved for smoking cessation by the U.S. Food and Drug Administration (FDA) for individual who smoke and use e-cigarettes.

Previous randomised controlled trials (RCTs) have indicated that varenicline - a partial, high-affinity $\alpha_4\beta_2$ nicotine receptor agonist is more efficacious than placebo, bupropion, and nicotine replacement therapies (NRTs) for smoking cessation.[23–25] The efficacy and safety of varenicline for smoking cessation in dual users has not been studied.

From a psycho-behavioral perspective, dual usage can be viewed as a manifestation of strong attachment to smokers' own tobacco cigarette brand, enabling the negotiations of social norms and antismoking restrictions.[26] Thus dual usage may potentially exacerbate nicotine dependence, prolonging the habit of smoking and hindering efforts to quit.[21,27] Nearly half of individuals who smoke and use e-cigarettes continue smoking and vaping over the course of a year, and 44% eventually return to exclusive smoking.[28,29] This suggests that the attachment to tobacco cigarettes in these individuals could be more pronounced than that of conventional smokers, leading us to hypothesise that the impact of varenicline may differ from what is typically observed in exclusive tobacco cigarette smokers.[30]

The aim of this double-blind randomised placebo-controlled trial was to evaluate the efficacy and safety of varenicline combined with smoking cessation counseling for adults who currently smoke cigarettes, use e-cigarettes, and intend to quit smoking. We also examined predictors for smoking abstinence.

Methods

Study design and participants

This was a double-blind, single-centre, RCT of the efficacy and safety, in addition to smoking counselling, of varenicline vs placebo in individuals who vaped and smoked and intended to quit smoking. Recruitment started in November 2018 (first participant first visit December 2018) and was completed in February 2020 (last participant last visit September 2020). The total duration of the trial was 24 weeks, comprised of a 12-week treatment phase directly followed by a 12-week non-treatment phase (Fig. 1). The study took place at Centro per la Prevenzione e Cura del Tabagismo (CPCT), the University-run smoking cessation centre.

Eligible participants were recruited from (1) local vape shops, (2) a local smoking cessation centre aimed at individuals who try to stop smoking by switching to e-cigarettes, (3) cessation and switching clinical research conducted by CoEHAR at the University of Catania, (4) social networks, (5) WhatsApp chat of the students of the University of Catania, and[5] word of mouth among relatives or friends of study participants. Adults who smoked at least one cigarette per day, used an e-cigarette at least once per day, and reported an intention to quit cigarette smoking were screened for eligibility.

Inclusion criteria were: (a) ≥18 years of age; (b) daily e-cigarette use for ≥12 months; (c) at least one tobacco cigarette smoked per day; (d) willingness to quit smoking, confirmed by a ''YES'' response to each of two questions ''Do you plan to quit smoking within the next 30 days?'' and ''Do you wish to participate in a smoking cessation programme?''; Exclusion criteria were: (a) current diagnosis of mental illnesses; (b) history of alcoholism or drug/chemical abuse within 12 months before screening; (c) known medical condition that, in the opinion of the investigators, would compromise participants' safety or participation; (d) currently pregnant or breast feeding or intending to become pregnant during the trial; (e) use of vaping products containing zero nicotine; (f) concurrent use of heated tobacco products.

The study is reported in line with the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines, and was performed in accordance with the Declaration of Helsinki and consistent with the regulatory principles of International Conference on Harmonization-Good Clinical Practice. The local ERB of the Azienda Ospedaliero Universitaria Policlinico (part of the Hospital Trust of Universita di Catania) reviewed and approved the study protocol (approval reference number: n.88/2016/PO, 11/07/2016) and written informed consent was received from all study participants. The study has been registered in EUDRACT, under the Trial registration ID: 2016-000339-42.

Due to poor recruitment, a change in the protocol was deemed necessary. The protocol amendment stipulated a change in the inclusion criteria (dual users intending to quit smoking instead of dual users intending to quit vaping) and consequently in the primary/secondary end points of the study (continuous abstinence from smoking in substitution of continuous abstinence from vaping; 7-day point prevalence of self-reported abstinence from cigarette smoking at 12-week and 24-week in substation of 7-day point prevalence of self-reported abstinence from e-cigarette use at 12-week and 24-week). The amendment was reviewed and approved by the local ERB (approval reference number: n.91/20l8/EMPO, 15/10/2018). All participants provided written informed consent.

Randomisation and masking

Varenicline (0.5 mg) and matched placebo tablets provided by the study sponsor (Pfizer Inc, USA) were packaged in glass containers by a local pharmaceutical company. Varenicline and placebo tablets secondary packaging were sent to the hospital pharmacy for

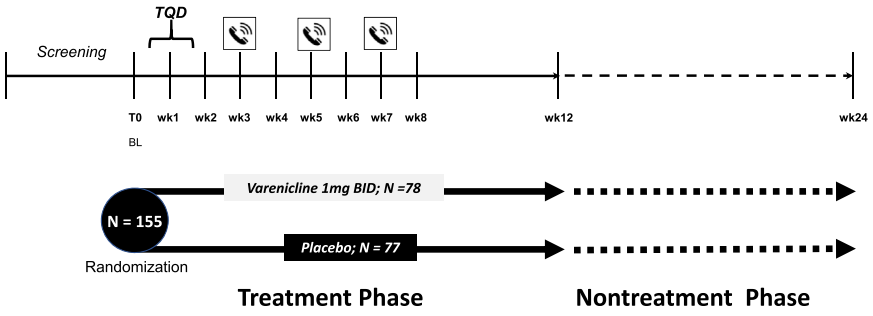

Fig. 1: Individuals who vape and smoke and intend to stop smoking were randomized to receive either varenicline, 1 mg, twice daily for 12 weeks or matched placebo for 12 weeks. Participants were prospectively reviewed for up to 24 weeks during which smoking and vaping habits, exhaled carbon monoxide levels, questionnaire scores, adverse events, vital signs, and body mass index were assessed at each study visit. Dashed lines indicate follow-up phase; telephone symbol, telephone contact.

double-blinding preparation. Labeling from the containers in the secondary package were removed and unlabeled study products were repackaged in coded containers. Blinding was ensured by the identical appearance of drug and placebo tablets and their containers. Eligible participants were randomly assigned (1:1) to receive either the active drug (varenicline) plus smoking cessation counseling or placebo plus smoking cessation counseling. The randomisation list for treatment assignment was generated using a SAS software (SAS Institute) by the hospital pharmacy staff. The fixed block size was n = 5 and the sequence of blocks was randomised and blinded. Participants, study staff and statistical team were blinded to randomisation and treatment assignment.

Study treatment

Participants in the varenicline group received varenicline (1 mg, administered twice daily for 12 weeks) plus counselling. Participants in the placebo group received placebo (administered twice daily, for 12 weeks) plus counselling. According to manufacturer's recommendations, participants assigned to varenicline were titrated to a full dose by the time of their TQD; they were started on 0.5 mg once daily for 2–3 days, then on 0.5 mg twice daily for 4–5 days, and finally on 1 mg twice daily for 11 weeks.

Participants in both treatment groups received the same smoking cessation counselling throughout the whole duration of the study. One-on-one counselling sessions were provided at each visit for a total of 10–15 min by two experienced clinical psychologists. Briefly, our approach to smoking cessation was partially adapted from the 5A's brief tobacco interventions for smokers who are ready to quit.[20,21] "Received intervention" indicates participants who were randomised to receive treatment (varenicline/placebo) and also underwent smoking cessation counselling. "Completed treatment phase" indicates participants who completed 12 weeks of interventions (i.e., varenicline/placebo + smoking cessation counselling). Study drug adherence was addressed by dosing record checks at each study visit. All the activities carried out during study visits are listed in eTable 1 (see Appendix).

Study procedures

At the baseline visit (V1), eligibility criteria were reassessed and participants were randomised as outlined above. The following data were recorded at V1: sociodemographic characteristics, medical history, smoking and vaping history (including type of device, and pattern of use), cigarette and e-liquid consumption, exhaled carbon monoxide (eCO) levels, blood pressure, heart rate, weight/Body Mass Index (BMI), questionnaires' scores (Fagerstrom test for cigarette dependence—FTCD)–[31]; Beck Depression Inventory-II–BDI-II[32]; Beck Anxiety Inventory—BAI[33]; Minnesota Nicotine Withdrawal Scale–MNWS),[34] level of motivation to quit smoking (assessed by visual analogue score–VAS),[35] and adverse events.

FTCD,[31] is a 6-item questionnaire used to measure the intensity of physical dependence related to cigarette smoking. The scores obtained on the test permit the classification of cigarette dependence into three levels: mild (0–3 points), moderate (4–6 points), and severe (7–10 points).

BDI-II,[32] is a 21-item questionnaire used to measures subjective rating of depression. Internal consistency for the BDI-II ranges from 0.73 to 0.92 with a mean of 0.86. The BDI-II demonstrates high internal consistency, with alpha coefficients of 0.86 and 0.81 for psychiatric and nonpsychiatric populations, respectively.

BAI,[33] a 21-item questionnaire used to rate subjective physiological and cognitive symptoms of anxiety. Each of the 21 BAI items is descriptive of a symptom of anxiety and is rated on a scale of 0–3. The BAI can be administered verbally by a trained interviewer or can be self-administered. The BAI has been found to discriminate well between anxious and nonanxious diagnostic groups and, as a result, is useful as a screening measure for anxiety in a variety of clinical populations. It has an

average reliability coefficient of 0.92 and a test–retest reliability of 0.75.

MNWS,[34] a 9-item questionnaire used to evaluate nicotine withdrawal symptoms. The MNWS reflects a range of withdrawal symptoms including craving, sleep disturbances, and physiological symptoms. The withdrawal syndrome is made up of a series of symptoms that occur after cessation of smoking, characterised by irritability, anxiety, nocturnal awakening, depression, difficulty concentrating, hunger, restlessness, impatience, and a strong desire (i.e., craving) for nicotine.

Level of motivation to give up smoking was captured using a 10-point visual analogue scale (VAS) with 1 being 'very low' and 10 being 'very high'.[35]

After Visit 1 (V1), participants were invited to return to the clinic on a weekly basis for the following 12 weeks (Visit2-Visit10), except for Visits 4, 6, and 8 (telephone contact). At each visit, participants underwent smoking cessation counseling. Cigarette and e-liquid consumption, exhaled carbon monoxide (eCO) levels, blood pressure, heart rate, weight/Body Mass Index (BMI) (only at Week-12 visit), MNWS (only at Week-1, -2, -4, -6, -8, -12 visit), and adverse events were recorded in the Case Report Form (CRF) at each study visit. Study drugs were dispensed before check-out in accordance with the plan (Appendix; eTable 1).

The study was continued in the non-treatment follow-up phase after completion of the treatment phase, consisting of a clinic visit at week-24 (V11). Cigarette and e-liquid consumption, eCO levels, blood pressure, heart rate, weight/BMI and MNWS were recorded in the CRF at this study visit.

Study endpoints

The primary efficacy endpoint of the study was the proportion of participants with biochemically validated continuous abstinence from smoking between week 4 and week 12 (continuous abstinence rate–CAR 4–12). Continuous abstinence from smoking was defined as eCO-verified (<10 ppm) self-reported abstinence from cigarette use after quit date at each study visits, from week-4 throughout week-12 (CAR 4–12). CAR weeks 4–12 was used to compare quit rates between varenicline and placebo. Timeframe of the reported abstinence for CAR was "since previous study visit".

The secondary efficacy endpoints were eCO-verified (<10 ppm) self-reported complete abstinence from cigarette use after quit date at each study visits, from week-4 throughout week-24 (CAR 4–24) and the 7-day point prevalence of smoking, biochemically confirmed by eCO (<10 ppm), abstinence at week 12 and at week 24. Smoking reduction is defined as a self-reported ≥50% reduction in the number of cigarette smoked per day from baseline. Smoking relapse is defined as a self-reported cigarette use after a period of smoking abstinence.

Safety endpoints included information on the number of adverse events (AE), and serious adverse events (SAE) occurring between treatment randomisation (V1) and last week of treatment (V10). Between and within treatment groups changes were reported for blood pressure, heart rate, weight, and BMI. Secondary analyses by smoking phenotype classification (continuous quitters vs treatment failures, which includes anyone that does not fall under the CAR definition; i.e., failures, relapsers, and lost to follow up), will be reported separately.

Safety reporting

Safety data were summarised for both treatment groups and summary statistics reported. Any events documented in the period from the point of treatment initiation until last week of treatment (week-12, V10) was considered relevant to the safety analysis. AEs and SAEs, regardless of treatment group or suspected causal relationship to study drug, were recorded. Sufficient information was obtained by the investigators to determine the causality of the AEs/SAEs.

Statistical methods

No success rates of varenicline among adults who smoke cigarettes and use e-cigarettes were available to determine an adequate sample size for this study, the first of its type. In the absence of an identical prior study, the power calculation was based on an assumed parity with the study of Ebert et al.[36] We firstly considered that population of light smokers to be a good proxy for the dual users in our trial. Ebbert et al.[36] published an RCT comparing the use of varenicline + counseling vs placebo + counselling in 93 light smokers. In the paper of Ebbert et al., at 12 weeks (end-of-treatment), the prolonged smoking abstinence rate was 40.0% in the varenicline group compared to 8.3% in placebo (OR: 7.33, 95% CI: 2.24–23.98), and at 26 weeks (end-of-follow-up) was 31.1% and 8.3%, respectively (OR: 4.97, 95% CI: 1.49–16.53). The primary efficacy endpoint of our study was the proportion of participants with biochemically validated continuous abstinence from smoking between week 4 and week 12. This is a more demanding efficacy endpoint than that of prolonged abstinence definition used by Ebbert et al. Given that are actually differences in both populations and outcomes definitions between the Ebbert et al. and our study, a conservative approach was adopted, with the largest calculated sample size across a range of possible estimates being selected. The final sample size chosen was based on a 90% power to demonstrate a placebo-corrected effect size of 22.8% for prolonged abstinence at 26 weeks at a significance level of $P < 0.05$. Using the method of Machin et al.[37] and a chi-squared distribution, a required base sample size of 62 patients per arm was

estimated. Allowing for up to 20% drop-out rate in each arm, this yielded a final total sample size of 155 patients. The sample size calculation table has been included (see Appendix).

Summary descriptive statistics are reported for each treatment group. Between group differences for quantitative variables were evaluated by one-way analysis of variance (ANOVA) and Mann–Whitney U test for normally and non-normally distributed data, respectively. χ^2 test was used to test differences on categorical variables. Intention-to-treat analyses were adopted for efficacy evaluation, on the assumption that participants lost to follow-up continued smoking. Per-protocol analyses were performed for between groups comparison of vital signs and body weight/BMI. OR and 95% CI were calculated according to Altman[38] and χ^2 test was used to evaluate association in the contingency tables. Continuous abstinence rates (n = 2; week 12 + week 24) and 7-day point prevalence (n = 7; weeks 4, 5, 6, 7, 8, 12 & 24) were reported with adjusted P-values using the Holm-Bonferroni method for multiple testing.

Lost to follow-up participants were addressed via best/worst case imputation in a sensitivity analysis. In the best-case scenario, all dropouts from the Varenicline group were assumed to be abstinent, while in the worst-case scenario, all dropouts from the Placebo group were assumed to be abstinent. This analysis is considered exploratory and no adjustments for multiple testing were made for continuous abstinence rates.

Safety data were summarised for both treatment groups and summary statistics reported. Any events documented in the period from the point of treatment initiation until last week of treatment (week-12, V10) was considered as relevant to the safety analysis.

To identify possible predictors of continuous abstinence from smoking, a multiple logistic regression model was estimated in which CAR 4–12 (yes/no) was entered as the dependent variable. Possible predictors of continuous abstinence, were entered in the model as independent variables and included age, gender, years of smoking, years of dual usage, cigarettes smoked per day, FTCD score, motivation levels by VAS, BDI II score, BAI score, education level, marital status, cohabitant smokers, previous quit smoking attempts, and study groups. Z-test was used to determine the effect of the predictor variables on the primary endpoint (i.e., CAR 4–12) in the logistic regression model.

The analyses were performed using Python 3.6 with Pandas 1.3.5, SciPy 1.7.3 and Statsmodel 0.12.2, and jamovi 2.3.16.

Role of the funding source

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Results

Of 371 consecutive participants assessed for eligibility, 195 were excluded (140 single users, 29 unwilling to quit smoking, 19 declined to participate, 4 also using heated tobacco products, 2 treated for major depressive disorders, 1 using zero nicotine e-cigarettes) and 21 did not attended their scheduled baseline visit. The remaining 155 participants were randomly assigned to receive either varenicline (n = 78) or matched placebo (n = 77). The flow diagram of study participants' participation in the trial is shown in Fig. 2. One hundred and fourteen participants completed all the visits within the treatment phase (initial 12 weeks), of whom 61 were in the varenicline group and 53 in the placebo group. Of note, 14 participants discontinued treatment in varenicline group and 18 participants discontinued treatment in placebo group. The non-treatment phase (additional 12 weeks) was completed by 88 participants, of whom 52 were in the varenicline group and 36 were in the placebo group.

Participants' baseline characteristics (Table 1) between groups were comparable with the exception of their quitting smoking motivation and education level. Study participants had a mean (SD) age of 52.8 (9.4) years, and smoked a mean (SD) of 9.2 (2.4) cigarettes/day. Participants were dual users for at least 1 years, of which 54.8% having made >2 serious quit smoking attempts in the past. Their mean (SD) FTCD score was 6.1 (1.6) for the varenicline group and 5.9 (1.8) for the placebo group, indicating a moderate level of cigarettes dependency. Nonetheless, their level of motivation to quit was on average very high (with a median score of 9.5 and 8 for those in the varenicline and in the placebo group, respectively) indicating strong motivation to quit.

Approximately, more than 80% of study participants used a refillable vaping product (Table 1). Mean (SD) e-liquid consumption at baseline was 1.7 (1.3) and 1.8 (1.3) ml/day for participants in the varenicline and placebo group, respectively (Table 2). Participants in the varenicline study group increased their e-liquid consumption up to 64.7% whilst reducing daily cigarette consumption by 56.5%. In the placebo study group daily cigarette consumption remained stable throughout the study and no increase in e-liquid consumption was observed. These findings may suggest a substitution/compensatory effect.

The eCO-verified CARs for weeks 4–12 and weeks 4–24 are shown in Fig. 3 and Table 3. We found that the CARs were significantly higher for the varenicline group vs the placebo group at each interval: 50.0% vs 16.9% (OR = 4.9; 95% CI, 2.3–10.4; P < 0.0001) at weeks 4–12; and 48.7% vs 14.3% (OR = 5.7; 95% CI, 2.6–12.3; P < 0.0001) at weeks 4–24. The 7-day point prevalence of smoking abstinence was also significantly higher for the varenicline group than the placebo group at each time point (Table 2); 51.2% vs 22.0% (OR = 3.7, 95%

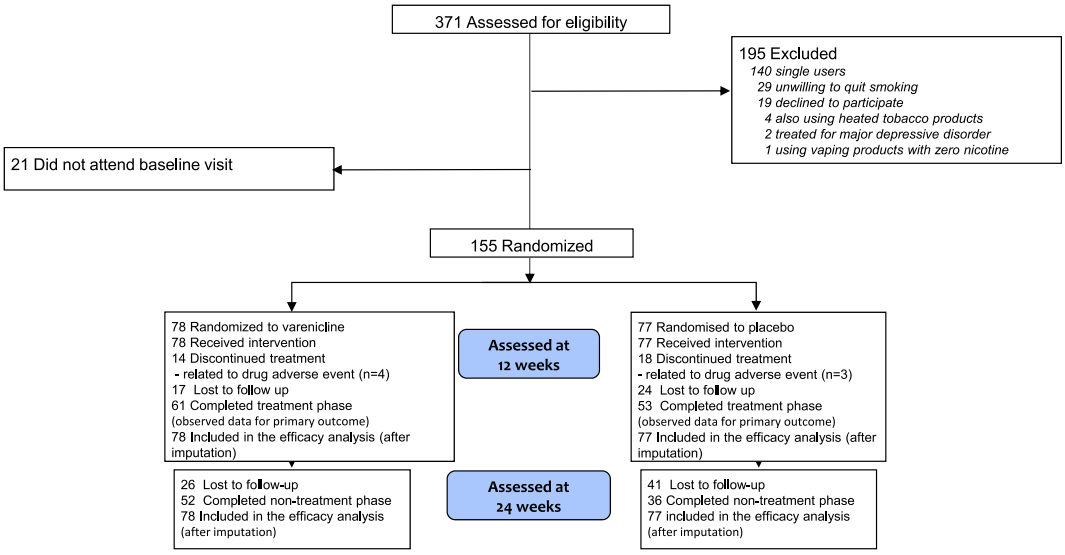

Fig. 2: Study flow diagram of subjects assessed for eligibility and included in the trial.

CI = [1.9–7.5]; P = 0.0008) at week 12; and 48.7 vs 18.1 (OR = 4.3, 95% CI = [2.1–8.9]; P = 0.0003) at week 24.

Details of changes in smoking status at each study visit are illustrated in Appendix; eTable 2. Smoking reduction and smoking relapse rates were calculated by considering changes in smoking behaviour trajectories.

Taking the whole cohort of participants completing the study (n = 114 at 12 week; n = 88 at 24 week), reduction in smoking consumption was observed in 25.4% and 18.2% of the participants at week 12 and week 24, respectively. The number of cigarette reducers between study groups was significantly different only at week 24 after stopping treatment (33.3% vs 7.7% for placebo and varenicline, respectively; P = 0.0007) (Appendix; eTable 2).

Taking the whole cohort of participants completing the study, smoking relapse was observed in 24.6% and 22.7% of the participants at week 12 (V6) and week 24 (V7), respectively. For the *intention-to-treat* analysis, smoking relapse rate considered behaviour trajectories from V5 to V6 (for changes occurring in week 8–12), and from V6 to V7 (for changes occurring in week 12–24) (Appendix; eTable 2). Specifically, variations in the total number of relapsing smokers were calculated by also adding the increase in number of LTFUs and then dividing the total number of participants. We observed a three-fold increase in smoking relapse rate after drug withdrawal in the varenicline group from 5.1% (from V5 to V6) to 15.4% (from V6 to V7) (P = 0.0002). No significant changes were found in the placebo group after drug withdrawal (Appendix; eTable 2).

Among cigarette quitters, a small number of participants also quit using e-cigarettes by the end of the study (accidental e-cigarette quitters; n = 6, 2 in the placebo group and 4 in the varenicline group).

A multiple logistic regression model was used to estimate the effect of several factors on smoking abstinence (Appendix, eTable 3). The results showed that the odds ratio (OR) for the CAR at weeks 4–12 was 4.4 (95% CI, 1.9–10.1; P < 0.001) in the varenicline group compared to the placebo group (Appendix; eTable 3). Be Male reduced the odds of success for CAR by approx. 60% (OR, 0.4; 95% CI, 0.17–0.97; P = 0.042). Having low mood as assesed by BDI reduced the odds of success for CAR by approximately 80% (OR, 0.212; 95% CI, 0.061–0.73; P = 0.014).

Sensitivity analyses were carried out, with best/worst case imputation, considering all dropouts in Varenicline group as abstinent and all dropouts in Placebo group as smokers and vice versa (Appendix, eTable 6).

The total number of AEs was significantly greater in the varenicline group than in the placebo group (253 vs 139: P = 0.017). AEs were rated as mild or moderate and rarely led to treatment discontinuation; four in the varenicline group and three in the placebo group.

The AEs that occurred more frequently in the varenicline group than in the placebo group were nausea (58 [23.1%] vs 23 [16.5%]), abnormal dreams (19 [7.6%] vs 6 [4.3%]), and flatulence (18 [7.2%] vs 6 [4.3%]) (Appendix; eTable 4). The frequency of most commonly reported oral/respiratory AEs (such as dry mouth, and cough) was reduced by the end of the study, lower in the varenicline compared with the placebo group.

No significant changes in mean (SD) vital signs from baseline were observed between and within treatment groups at Week 12 (Appendix; eTable 5A). With the exception of a small decrease in systolic blood pressure

	Varenicline group (N = 78) mean (±SD)	Placebo group (N = 77) mean (±SD)
Characteristic		
Age (years)	51.8 (10.3)	53.9 (8.3)
Years of smoking[c]	28.4 (8.0)	27.8 (9.6)
No. of cigarettes smoked per day	9.2 (2.4)	9.1 (2.3)
Years of dual usage[d]	1.5 (0.9)	1.4 (0.9)
E-liquid consumption (ml/die)	1.7 (1.3)	1.8 (1.3)
Motivation level by VAS score	9.5 (8–10)[a]	8 (7–10)[a]
BDI score	7.5 (4–11.75)[a]	8 (4–14)[a]
BAI score	6 (4–12.75)[a]	7 (2–13)[a]
FTCD	6.1 (1.6)	5.9 (1.8)
MNWS[b]	3 (2–5)[a]	3 (0–7)[a]
Weight (kg)	77.7 (13.5)	80.2 (14.2)
Height (cm)	176.8 (10.7)	179.2 (8.4)
BMI	26.1 (4.8)	27.3 (3.5)
SBP (mmHg)	125.4 (17.9)	128.8 (16.4)
DBP (mmHg)	78.6 (11.1)	79.5 (12.6)
HR (b/min)	75.7 (9.8)	76.9 (9.9)
	No. (%)	No. (%)
Gender		
M	44 (56.4%)	52 (67.5%)
F	34 (43.6%)	25 (32.5%)
Marital status		
Married	54 (69.2%)	62 (80.5%)
Unmarried	16 (20.5%)	8 (10.4%)
Divorced	4 (5.1%)	4 (5.2%)
Widower	2 (2.6%)	3 (3.9%)
Cohabiting	2 (2.6%)	0 (0%)
Education level		
No education	0 (0%)	1 (1.3%)
Elementary school	6 (7.7%)	10 (12.9%)
Middle school	20 (25.6%)	34 (44.2%)
High school	38 (48.7%)	24 (31.8%)
Graduation	14 (17.9%)	8 (10.4%)
Cohabitant smokers		
Yes	44 (56.4%)	49 (63.6%)
No	34 (43.6%)	28 (36.4%)
Previous quit smoking attempts[e]		
Yes	45 (57.7%)	40 (51.9%)
No	33 (42.3%)	37 (48.1%)
Main vaping device[f]		
Refillable tank	55 (70.5%)	56 (72.7%)
Refillable pod/cartridge	10 (12.8%)	10 (13.0%)
Closed pod/cartridge system	10 (12.8%)	9 (11.7%)
Disposable	3 (3.9%)	2 (2.6%)

[a]Median (IQR). [b]MNWS, measured at week-4 (varenicline, n = 66; placebo, n = 63). [c]Previous years of tobacco cigarette smoking, including years of dual usage. [d]Years of daily dual usage. [e]More than 2 serious quit attempts in the past. [f]A secondary device was used in 12.8% and 10.4% of cases in the varenicline and placebo group, respectively.

Table 1: **Baseline characteristics of study participants by treatment group.**

within the placebo group, there were no significant changes in mean (SD) cardiovascular parameters between and within treatment groups at Week 24 (Appendix; eTable 5B). However, significant changes in weight and BMI from baseline were observed at week 24. A net weight gain of 3.4 kg and increase in BMI of 1.5 points were observed within the varenicline group (P = 0.023 and P = 0.033 for weigh and BMI respectively). These changes were still significant when compared to those observed in the placebo group

Study product study visits	Study group varenicline						Study group placebo					
	V1 base	V5 Wk4	V7 Wk6	V9 Wk8	V10 Wk12	V11 Wk24	V1 base	V5 Wk4	V7 Wk6	V9 Wk8	V10 Wk12	V11 Wk24
Cigarette consumption												
Mean cigarette/day (±SD)	9.2 (2.4)	4.6 (2.0)	4.1 (1.8)	4.0 (1.8)	4.2 (1.9)	4.7 (2.1)	9.1 (2.3)	6.3 (2.6)	7.1 (3.2)	6.1 (2.6)	7.3 (2.3)	7.4 (2.5)
E-liquid consumption												
Mean ml/day (±SD)	1.7 (1.3)	2.4 (1.9)	2.5 (1.9)	2.8 (2.2)	2.7 (2.3)	2.8 (1.9)	1.8 (1.3)	2.0 (1.6)	1.8 (1.5)	2.0 (1.3)	1.7 (1.3)	1.8 (1.4)

[a]Attending each and all study visits.

Table 2: **Consumption data for trial participants.**[a]

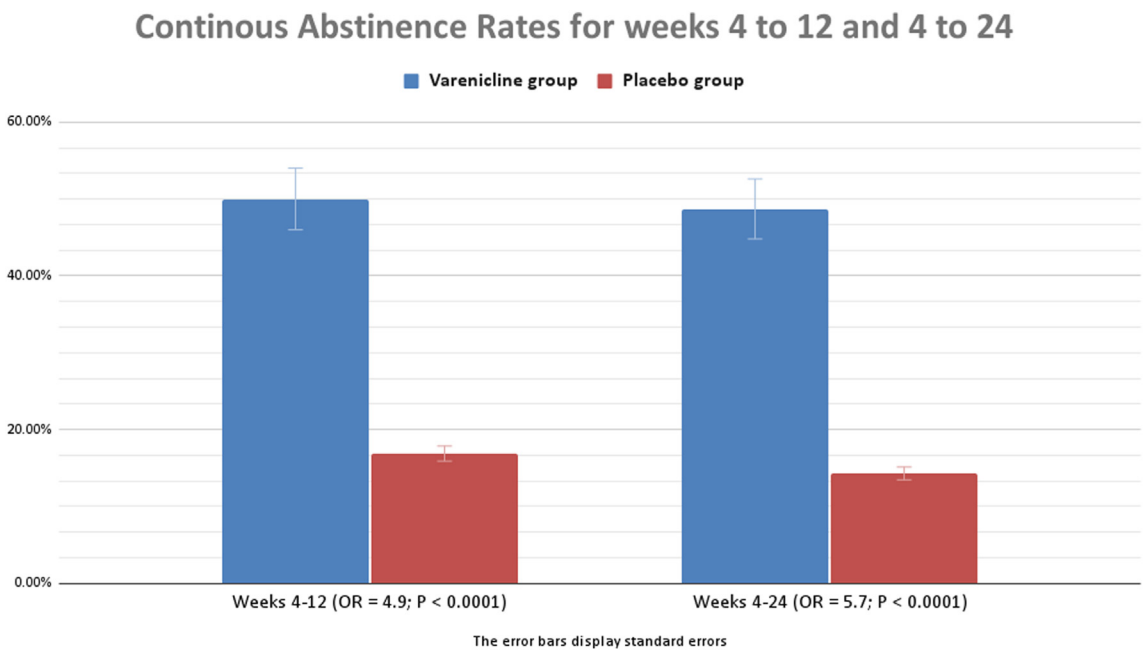

Fig. 3: Continous abstinence rates at weeks 4–12 (CAR 4–12) and 4–24 (CAR 4–24) in dual users randomized to varenicline. Proportion of participants who reported abstinence from smoking was defined by exhaled carbon monoxide level–verified (<10 ppm) self-reported abstinence. The bars in the Figure indicate standard errors.

	Varenicline group	Placebo group	OR	95% CI	Adjusted P-value
Continuous abstinence rate					
CAR 4–12 weeks	50.0%	16.9%	4.9	[2.3–10.4]	0.00001265
CAR 4–24 weeks	48.7%	14.3%	5.7	[2.6–12.3]	0.000008064
7-day point prevalence					
Week-4	55.1%	29.8%	2.9	[1.5–5.6]	0.004422
Week-5	53.8%	32.4%	2.4	[1.3–4.7]	0.014448
Week-6	55.1%	22.0%	4.3	[2.2–8.7]	0.00016821
Week-7	56.4%	27.2%	3.6	[1.8–6.8]	0.0009492
Week-8	55.1%	33.7%	2.4	[1.3–4.6]	0.014448
Week-12	51.2%	22.0%	3.7	[1.9–7.5]	0.000816
Week-24	48.7%	18.1%	4.3	[2.1–8.9]	0.00034068

P-values adjusted using the method of Holm-Bonferroni [Holm S. Scand J Stat 1979; 1:65–70].

Table 3: **Continuous abstinence rates and 7-day point prevalence.**

(P = 0.041 and P = 0.025 for weigh and BMI respectively).

Of interest, MNWS-increased appetite scores for participants in the varenicline group was significantly increased compared to participants in the placebo group; increased appetite (MNWS-increased appetite scores ≥1) at week 12 was reported in 28.9% and 15.1% of participants for varenicline and placebo respectively (P = 0.032). Similar findings were also observed at earlier time-points.

Measures of urge to smoke across the treatment phase of this study were consistently attenuated with varenicline; at week-4, average MNWS craving sub-score of 0.42 (SD = 0.58) in the varenicline group was significantly lower than 1.3 (SD = 1.51) (P < 0.0001) in the placebo group.

Discussion

Many individuals that vape and smoke express the interest in receiving professional help for smoking cessation,[39] thus there is a need for treatment protocols and guidelines to advance best practice and outcomes for people who vape and smoke and who want to quit. However, there is lack of information on effective strategies and interventions to promote smoking cessation among dual users. Specific studies are needed to investigate the effectiveness of interventions tailored to the needs of individuals who smoke and use e-cigarettes and intend to quit smoking cigarettes.

This RCT was the first to explore the effectiveness and safety of varenicline, 1 mg taken twice daily, as a smoking cessation aid for adults who smoke and use e-cigarettes. The study findings indicate that varenicline can help them quit smoking, leading to prolonged abstinence from tobacco cigarette use. Despite the results also showed significant differences in adverse events between treatment groups, the study showed a good safety profile for varenicline even in individuals who vape and smoke and these findings are consistent with earlier data from an exploratory study suggesting that varenicline use may promote success in quitting smoking among dual users.[39]

The odds ratios in the varenicline group of established dual users exceeded those reported in RCTs for smoking cessation in smokers in the general population.[23,24] This discrepancy could be attributed to participants' elevated motivation levels and the reported compensatory or substitution effect resulting from increased e-cigarette usage within the varenicline arm of the study (see Table 2). Interestingly, the OR for CAR 4–24 was even higher than that for CAR 4–12. This finding may be also linked to the compensatory/substitution effect stemming from increased e-liquid consumption. In summary, these results suggest that individuals who both smoke and use e-cigarettes may have a more favorable chance of quitting smoking compared to those who exclusively smoke conventional cigarettes.

Varenicline is a specific partial agonist and antagonist of the α4β2 nicotinic acetylcholine receptor that has been found to be effective in increasing abstinence rates among cigarette smokers. It is expected to help adults who smoke and use e-cigarettes quit cigarette smoking in light of its mechanism of action that attenuates withdrawal symptoms and craving.[40,41] In line with these observation in cigarette smokers, varenicline was shown to be consistently effective at reducing urge to smoke in dual users. Another mechanism by which varenicline facilitates sustained abstinence is by reducing the likelihood of relapse to smoking during a quit attempt.[23,24,42] Although relapse prevention was not formally investigated, this effect of varenicline was confirmed in the present study. After participants in the varenicline group stopped using the drug (between weeks 12 and 24), a three-fold increase in smoking relapse rate was observed compared to the placebo group (see eTable 2). Nevertheless, the relapse rate remained low in comparison to other similar studies. This could be explained by the fact that concurrent use of e-cigarettes acted as an effective protective factor against relapse to tobacco cigarettes.[43]

Similar to what is observed in cigarette smokers[33,44] high level of depressive symptoms (as assessed by BDI) and be male reduced the odds of success for abstinence from tobacco cigarettes also in individuals who smoke and use e-cigarettes. The presence of depressive symptoms and factors related to gender are known to be among the strongest predictors of poor success in quitting smoking among adult cigarette smokers.[44–46]

The safety profile of varenicline in this study was good and similar to that of previous varenicline trials of smokers in the general population.[23,24] A gradual gain in weight and BMI was observed in the varenicline but not in the placebo group. This is not surprising and probably due to the higher prevalence of smoking quitters among the active group as weight gain often occurs after smoking cessation.[47,48]

This RCT has several strengths: 1) use of continuous abstinence rate as a robust primary efficacy endpoint of the study; 2) use of CO measurements to objectively verify smoking abstinence; 3) careful verification of compliance with study medications attained by drug adherence checks; and 4) detailed characterisation of study participants, that include their dual usage patterns and details of their vaping products. Despite these strengths, the study has several limitations. First, findings in a population of adults who smoke and use e-cigarettes cannot be extended to young dual users. Second, findings were restricted to a selected population of participants who had a strong desire to stop smoking and used by and large refillable vaping products, thus limiting the generalisability of the results. Third, the

short duration of the follow-up of the study is inadequate to establish the full potential of the intervention and longer follow-up should be considered in future studies. Lastly, the impact of smoking cessation counseling could not be assessed as the study was not designed to test the isolated effect of the behavioural intervention.

The findings of the present RCT indicate that inclusion of varenicline in a smoking cessation programme for adults who vape and smoke and intend to quit may result in prolonged abstinence without major adverse events. This evidence supports the use of varenicline in cessation programmes to help people who smoke and use e-cigarettes quit smoking and may inform future recommendations by health authorities and healthcare providers. Studies with longer follow-up should be conducted to evaluate long-term efficacy.

Contributors

PC, PMR, and CFL had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: PC, LS, DC, RP. Acquisition, analysis, or interpretation of data: PC, PMR, CFL, MM, DC. Drafting of the manuscript: PC, DC, PMR, CFL, LS, GC, RP. Critical revision of the manuscript for important intellectual content: PC, LS, JSA, CR, MCQ, MSS, RP. Statistical analysis: PMR, and CFL. Obtained funding: PC, RP. Administrative, technical, or material support: PC, MM, RP. Supervision: PC, DC, RP. PC, PMR, CFL, and RP accessed and verified the underlying data and led the development of the manuscript. All authors read the manuscript, provided critical input, and approved the final manuscript.

Data sharing statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declaration of interests

RP is a full tenured professor of Internal Medicine at the University of Catania (Italy) and Medical Director of the Institute for Internal Medicine and Clinical Immunology at the same University. He has received grants from U-BIOPRED and AIR-PROM, Integral Rheumatology & Immunology Specialists Network (IRIS), Foundation for a Smoke Free World, Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, Merk Sharp & Dohme, Boehringer Ingelheim, Novartis, Arbi Group Srl., Duska Therapeutics, Forest Laboratories, Ministero dell Universita' e della Ricerca (MUR) Bando PNRR 3277/2021 (CUP E63C22000900006) and 341/2022 (CUP E63C22002080006), funded by NextGenerationEU of the European Union (EU), and the ministerial grant PON REACT-EU 2021 GREENBando 3411/2021 by Ministero dell Universita' e (MUR)—PNRR EU Community. He is the founder of the Centre for Tobacco Prevention and Treatment (CPCT) at the University of Catania and of the Centre of Excellence for the Acceleration of Harm Reduction at the same university. He receives consultancy fees from Pfizer, Boehringer Ingel-heim, Duska Therapeutics, Forest Laboratories, CV Therapeutics, Sermo Inc., GRG Health, Clarivate Analytics, Guidepoint Expert Network, and GLG Group. He receives textbooks royalties from Elsevier. He is also involved in a patent application for ECLAT Srl. He is a pro bono scientific advisor for Lega Italiana Anti Fumo (LIAF) and the International Network of Nicotine Consumers Organizations (INNCO); and he is Chair of the European Technical Committee for Standardization on "Requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437; WG4). PC has been affiliated to the CoEHAR since December 2019 in a pro bono role. He is co-author of a protocol paper supported by an Investigator-Initiated Study award programme established by Philip Morris International in 2017. In the past 3 years, CR's organisation, Russell Burnett Research and Consultancy Ltd, has received research funding and/or consultancy fees from Cheerain HK Ltd, McKinney Regulatory Science Advisors LLC, Los Angeles Clinical Trials LLC, Health Diplomats, Centre for Substance Use Research Ltd, whatIF? Consulting Ltd, British American Tobacco, Rogue Holdings LLC, Japan Tobacco International, NJOY LLC, SkyX Group Inc, and ECLAT Srl to conduct or consult on perception and behavioral research of non-combustible tobacco and nicotine products. CR also holds stock options in SkyX Group Inc. JSA received sponsored funds for travel expenses as a speaker for the 2021 and 2022 annual GTNF conference. JSA serves as a consultant and has equity in Qnovia, a start-up company. All other authors have no competing interests to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102316.

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