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Protocol

An exploratory, randomised, crossover study to investigate the effect of a nicotine containing electronic cigarette on appetite in healthy adult smokers, after a period of smoking abstinence: study protocol

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ABSTRACT

Background: Many individuals continue to smoke despite the known harmful effects of cigarette smoking. Tobacco harm reduction (THR) is a public health strategy that seeks to reduce or prevent projected harm caused by cigarette smoke via encouraging smokers, who would otherwise continue to smoke, to switch to products with reduced risk profiles (such as e-cigarettes). Research shows smoking can influence numerous physiological and psychological functions such as appetite, cognitive function and emotion. For some smokers, the loss of such effects upon cessation has been cited as an incentive to resume smoking. The effect of e-cigarettes (and other non-combustible alternatives to cigarette smoking) on the above-described physiological and psychological functions has not been widely researched. Such information may be important for more thoroughly evaluating the proposition that smokers seeking alternatives may find e-cigarettes a satisfactory substitute for conventional cigarettes.
Methods: This randomised, partially blinded, crossover study will test the hypothesis that use of a nicotine containing e-cigarette can influence appetite to the same extent as a combustible cigarette following a period of nicotine abstinence in current smokers. Up to 40 current smokers will be recruited into the study. Enrolment started in February 2021 and the results from the study are expected in 2022.
Conclusions: The data from this study will be a valuable addition to the growing body of literature about the potential of e-cigarettes as a satisfactory and viable long-term alternative to cigarettes for existing smokers.
Trial Registration: This study is registered with the ISRCTN registry, number ISRCTN72435551.

Keywords: Nicotine, E-cigarette, Appetite, Smoking cessation, Tobacco harm-reduction

INTRODUCTION

Cigarette smoking is widely recognised as a leading avoidable cause of disease, including lung disease, cardiovascular disease and cancer. Despite the number of smokers globally decreasing in recent decades, the World Health Organization (WHO) has reported that there are still more than 1 billion tobacco smokers worldwide.[1] To reduce the projected negative health burden from cigarette smoking as a public health priority, there has been a global response from regulators and educational tobacco control initiatives worldwide.[1] One such strategy that aims to reduce or prevent the harm caused by cigarette smoking is tobacco harm reduction (THR), the substitution of cigarettes with non-combustible alternatives such as electronic cigarettes (e-cigarettes) or tobacco heating products (THPs).[2]

E-cigarettes (also termed electronic nicotine delivery systems (ENDS)) are a powerful tool for THR as numerous studies have demonstrated that in comparison to cigarette smoke, the aerosol from an e-cigarette contains significantly lower quantities and levels of chemical toxicants.[3-4] This is because e-cigarettes operate without combustion, instead, an aerosolised carrier, such as vegetable glycerine and/or propylene glycol is utilised and heated to turn the e-liquid into a vapour.[2] Detailed reviews of the scientific evidence for e-cigarettes have been conducted by both the UK Royal College of Physicians and Public Health England, concluding that e-cigarette use is approximately 95% less harmful than cigarette smoking.[5-7] However, smoking rates in the UK remain at 14.7%.[8]

Cigarette smoking is associated with a range of physiological and psychological effects including effects on body weight, emotion and cognitive function.[9,10] Published scientific evidence suggests that smoking can influence numerous elements of body weight maintenance including appetite and metabolism.[11] Weight gain following smoking cessation, known as post-cessation weight gain (PCWG), is a common occurrence, with a typical mean weight gain after 12 months of smoking abstinence of 4-5kg.[12] Along with other effects, such as perceived deficit in cognitive function, PCWG has been cited as a reason for resumption of smoking post-cessation.[13-15] Whilst not positioned as cessation devices, the direct effect of e-cigarettes (and other alternatives to cigarette smoking) on such functions has not been widely researched and is not well understood. This information may be important for thoroughly evaluating the proposition that smokers seeking alternatives may find e-cigarettes a satisfactory substitute for conventional cigarettes. This study will be completed in conjunction with a separate study that will investigate if the acute delivery of nicotine through use of an e-cigarette can influence cognitive function in cigarette smokers during a period of smoking abstinence.[16]

The research methodologies applied in this study have been utilised widely in nutritional research, with the subjective appetite assessments and assessment of calorie consumption having been previously demonstrated to be sensitive to acute suppression of appetite due to a wide variety of interventions, including presence versus absence of tobacco smoking.[17-19] This approach has not however been utilised extensively to research differences between various nicotine-containing products and as such, the sensitivity of the approach to determine differences between nicotine containing products with different nicotine quantities and pharmacokinetic profiles, has yet to be fully evaluated.

The aim of this study is to test the hypothesis that use of a nicotine containing e-cigarette can influence appetite to the same extent as a combustible cigarette after a period of nicotine abstinence in current smokers.

METHODS

A redacted version of the full study protocol and statistical analysis plan (SAP) are provided in the supplementary information, submitted with this manuscript. The key aspects of the protocol are summarised below.

Study design and participants

The study will be a single-centre, prospective, randomised, partially blinded, crossover study performed in a purpose-built trial facility at Simbec-Orion (Merthyr Tydfil, UK). Eligible participants will be healthy adult current smokers.

Inclusion criteria

The inclusion criteria include healthy male or female participants, aged 25-45 years (inclusive), with a body mass index (BMI) of 18.5-29.9 kg/m^2 (inclusive), who are in good general health as confirmed via the principal investigator (PI). Subject must be a current smoker (self-reported consumption of at least 10 factory-made or self-rolled cigarettes per day) for 3 years or longer and be familiar with e-cigarettes (classified as use for at least 1 month in the previous 2 years). Smoking status will be confirmed via urinary cotinine sample (≥200 ng/ml). Subject must be willing to abstain from smoking, nicotine products, alcohol and caffeine (for 12 hours) and high-intensity exercise (for 24 hours) prior to each study session. The participants must be regular breakfast eaters and have no current diagnosis of any eating disorder.

Exclusion criteria

The exclusion criteria exclude participants with any acute illness such as respiratory tract infection or viral infection requiring treatment within 4 weeks prior to screening or upon admission. Any subjects who, prior to enrolment, are planning to quit/alter smoking/vaping usage within the duration of the study (to the follow-up telephone call) will be excluded. Any subject with clinically significant history of drug or alcohol abuse [defined as the consumption of more than 14 units of alcohol a week for male and female participants] within the past two years will be excluded. Additionally, participants who suffer from any food related allergies or have specific dietary requirements i.e., medical, social, cultural, or religious, that would preclude consumption of any standardised meals throughout the study will be excluded.

Randomisation and blinding

The randomisation schedule will be created by Simbec-Orion using a computer-generated pseudo-random permutation procedure in SAS version 9.4 and will determine the order in which participants are assigned to use each investigational product (or no product) during the study (Table 1). Codes will be produced based on

Williams Latin Square design for a five-by-five crossover with 10 sequences and four participants per sequence. Blinding will be applied to e-cigarette nicotine strength and will be maintained by participants being handed ready assembled devices.

Investigational product

The e-cigarette investigational product (Vype ePen3) is a commercially available, closed-system vapour device with a 650mAh rechargeable battery and associated 2.0 ml disposable cartridge containing e-liquid and a mouthpiece; manufactured on behalf of Nicoventures Trading Ltd, London, UK (cartridges for use in the study were assembled at BAT R&D, Southampton, UK to the commercial specifications). Each cartridge lasts for approximately 200 puffs with delivery of aerosol controlled to remain consistent throughout the charge/discharge cycle. The product was selected in part due to the known pharmacokinetic profile (the start of the subjective questionnaire assessment has been aligned with the product TMax).[20] E-liquids used in the study will contain 0, 12, or 18 mg/ml of protonated nicotine and will be Golden Tobacco flavour (Table 1). All participants will receive a demonstration and training at screening on how to correctly use the e-cigarette investigational product. The cigarettes to be used in the study will be commercially sourced Benson & Hedges Sky Blue king-size cigarettes, the market leading combustible cigarette in the UK (at time of study set-up).

Table 1: A table demonstrating the investigational products to be used within the study.

Product	Nicotine strength	Product usage
No product	N/A	N/A
E-cigarette	0 mg/ml	5 min *ad libitum*
E-cigarette	12 mg/ml	5 min *ad libitum*
E-cigarette	18 mg/ml	5 min *ad libitum*
Combustible cigarette	NA	1 stick 5 min *ad libitum*

Study objectives

Primary objective: to determine how use of a nicotine containing e-cigarette can influence appetite (calorie consumption) in regular smokers following a 12-hour period of nicotine abstinence compared to a combustible cigarette.

Secondary objective: to determine how use of a nicotine containing e-cigarette can influence subjective appetite and appetite hormone levels in regular smokers following a 12-hour period of nicotine abstinence compared to a combustible cigarette.

Exploratory objective: to determine how use of a nicotine containing e-cigarette can influence subjective mood and smoking urges in regular smokers following a 12-hour period of nicotine abstinence compared to a combustible cigarette.

Study endpoints

Primary endpoints: Ad libitum meal calorie consumption (calorie consumption).

Secondary endpoint(s): Leptin, ghrelin (active and total), insulin, glucose, peptide YY (PYY), glucagon-like peptide-1 (GLP-1: Active and total) and Visual Analogue Scale Subjective Appetite Questionnaire (eCOA).

Exploratory endpoint(s): Visual Analogue Subjective Emotion Questionnaire (eCOA), questionnaire on Smoking Urges (QSU) – Brief.

Other measures: Device mass loss by e-cigarette.

Measurement tools

Subjective measures and questionnaire data will be captured on the Cambridge Neuropsychological Test Automated Battery (CANTAB) Electronic Clinical Outcome Assessment (eCOA) platform (Cambridge Cognition, Cambridge, UK).

Study procedure overview

Screening will be overseen by Simbec-Orion site staff and will be conducted within 28 days of the first study session (for full screening procedures please refer to the study protocol, supplementary information). Eligible participants will be asked to return for each of the 5 study sessions and continued eligibility will be re-confirmed at each session. Participants will attend the clinical unit the morning before the study session, staying at the unit overnight (there will be 7 days between the start times of each study session). At study session 1 only, participants will be familiarised with the eCOA platform and asked to complete several baseline questionnaires. At all sessions, whilst resident at the clinical unit, participants will be provided a standardised lunch, dinner and snack before initiating a smoking, nicotine, alcohol and caffeine abstinence for a minimum of 12 hours prior to commencement of the study session the following morning. Whilst in the unit, participants will refrain from strenuous exercise.

On the morning of the study session, participants will be provided a standardised breakfast, consisting of a 250 ml orange juice, one yoghurt and one cereal bar (approximately 400 calories). The full breakfast is to be consumed within 15 minutes. Following a rest period of 115 minutes, participants will rate their alertness on the Karolinska Sleepiness Scale and caffeine urges on the Assessment of Caffeine Urges. Participants will then complete baseline questionnaires for emotion on the Subjective Emotion Questionnaire, appetite on the Subjective Appetite Questionnaire and smoking urges on

the Smoking Urges Questionnaire- Brief. Immediately after the rest period, participants will have a baseline blood sample taken and will be given their assigned investigational product to use *ad libitum* for 5 minutes. Participants will then complete a sub-set of questionnaires and additional blood samples at specific time intervals over a 60-minute period. A product satisfaction questionnaire will be performed (unless no product is assigned) at 15 minutes post-product use. Following the completion of study questionnaires, participants will be provided with an *ad libitum* meal consisting of a 500 ml bottle of water and a tray of three mini pizzas served at 10-minute intervals for 30 minutes. Participants will be instructed to "eat and drink until they feel comfortably full". Finally, after consumption of the meal, participants will repeat a sub-set of the questionnaires. A schematic of the Study Session schedule is presented in (Table 2).

Devices will be weighed immediately before and after use to allow for calculation of device mass loss (DML). Reading material will be provided for participants during the rest periods but the use of mobile phones or other personal electronic devices will not be permitted. Use of participants' own nicotine products will not be allowed until the completion of the study session. Follow-up interviews will be performed by telephone 5-7 days after the final study session. Participants will be able to withdraw from the study at any time and for any reason. It will be possible to remove individual participants from the study if he or she experiences an intolerable adverse event (AE), fails to meet the inclusion and exclusion criteria or deviates from the study protocol at any time (at the discretion of the PI). The study will be discontinued if any unacceptable safety findings are identified. The decision will be made, provided in writing and signed by the PI (or deputy) and the sponsor and provided to the research ethics committee. The sponsor may also temporarily suspend or prematurely discontinue the study at any time due to safety or ethical issues or severe non-compliance.

Safety and data quality assurance

To assess safety, all AEs that occur during the study period will be graded according to severity and recorded in the case report forms along with the date of onset, likely relation of the AE to the investigational product, resolution and product use, action taken and outcome if known. AEs will be coded in the system organ classes and preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0.

The study will be monitored by ORION Clinical Services Limited (Slough, UK). The monitor will make regular visits to the study site to check the completeness of master files and study records, accuracy of reporting on the case report forms and adherence to the protocol. Other checks will be progress of enrolment and storage, handling and accountability of the investigational products. Direct access to relevant anonymised clinical records to confirm their consistency with the data in the case report forms may be granted by the PI to the study monitor, auditor(s), research ethics committee and the UK Medicines and Healthcare products Regulatory Agency. All study files and documentation will be archived for at least 25 years after the end of the study in line with the European Medicine Agency Guideline INS/GCP/856758/2018. Simbec-Orion will be responsible for maintaining participants' confidentiality.

Data captured in the case report forms will be provided to the Simbec-Orion statistics department as SAS datasets in a standard format that will be used for programming outputs. Questionnaire data will be sent by Cambridge Cognition to Simbec-Orion as an SAS dataset. The clinical database will be reviewed, all data issues resolved, the analysis sets approved and protocol deviation classifications agreed before database lock.

Statistical analysis

For the full statistical analysis approach, please refer to the SAP appended in the supplementary information.

Little information is available regarding variability and significant effect size in relation to the effect of nicotine on appetite. Data used from a previous crossover study, (n=10) assessing calorie intake after acute cigarette smoke exposure indicated 35 participants were considered to be significant to reject the null hypothesis.[21] To allow for a higher variability, dropouts or participants who otherwise fail to complete the study, 40 participants were enrolled onto the study. Analysis will be done on a per product basis in the per protocol population, which will include all participants who are assigned to the Analysis Set for an Investigational Product (IP) where they received the specific IP, have consumed the *ad libitum* meal and have calorie consumption data available, and did not violate the protocol (major protocol violation) in a way that may invalidate or bias the results.

Data on product history and use during the study will be presented as numbers and percentages. Continuous variables will be presented as means with standard deviations and medians with ranges. Categorical variables will be reported with numbers and percentages. Key outcome measures (highlighted in the SAP) for calorie consumption, concentrations of appetite hormones and subjective questionnaires will be reported with absolute and baseline-adjusted values (where appropriate) and will be listed and summarised by products using descriptive statistics N, n, mean, SE, SD, minimum, median and maximum. Statistical comparisons will be performed between products by ANOVA or ANCOVA on the absolute and baseline-adjusted results. Upon completion of the statistical analysis, additional ad hoc analysis may be justified that may inform future study designs in the field. All statistical analyses will be performed using SAS 9.4 or higher. Enrolment is complete and the results of this study are expected in 2022.

Table 2: Study flow and assessments.

Timepoint	Assessments
Overnight stay (10 hours)	Abstinence from nicotine, caffeine, alcohol and high-intensity exercise
Standardised breakfast (130 to 115 min)	N/A
First study session only (115 to 20 min)	Tobacco use history questionnaire
	Fagerström test for nicotine dependence (FTND)
	Dutch eating behaviour questionnaire (DEBQ)
	Caffeine consumption questionnaire (CCQ)
Baseline (20 to 15 min):	Karolinska sleepiness scale
	Assessment of caffeine urges
Baseline (15 to 5 min)	Subjective appetite questionnaire
	Subjective emotion questionnaire
	Questionnaire on smoking urges – brief
	Blood sample (hormone analysis)
Product use (5 to 0 min)	N/A
Product testing period (0 to 90 min)	Subjective appetite questionnaire
	Subjective emotion questionnaire
	Questionnaire on smoking urges-brief
	Blood sample (hormones analysis)
***Ad libitum* meal (70 to 100 min)**	Food intake
Post product testing	Product satisfaction questionnaire

DISCUSSION

Published scientific evidence suggests that smoking can influence various physiological and psychological functions (including appetite and metabolism).[9-11] For some smokers, potential weight gain post-cessation has been cited as a barrier to smoking cessation and PCWG has been shown to contribute to resumption of smoking.[22] The effect of e-cigarettes (and other alternatives to cigarette smoking) on such functions has not been widely researched but may be important in the acceptability of e-cigarettes as satisfactory substitutes for conventional cigarettes. A study by Jackson et al 2019 highlighted that approximately 1 in 8 smokers would be more likely to try e-cigarettes if evidence emerged that e-cigarettes could help control their weight.[23] The hypothesis of this study is that use of a nicotine containing e-cigarette can influence appetite to the same extent and same direction as a combustible cigarette after a period of nicotine abstinence in current smokers. To measure appetite an *ad libitum* meal consisting of oven cooked pizzas and 500 ml of water was chosen. This pizza was selected due to the lack of outer crust, to minimise the risk of participants eating energy-dense fillings and leaving the outside crust of pizza and therefore resulted in uniform energy density. If the hypothesis is confirmed, the findings would provide additional support for the proposition that smokers seeking alternatives may find e-cigarettes a satisfactory substitute for conventional cigarettes.

A crossover design was chosen because it permits the assessment of differences within individuals (reducing data variability). The BMI range 18.5-29.9 kg/m^2 (inclusive) is intended to minimise issues related to protocol adherence and other lifestyle factors.

Limitations

Cross-sectional studies have reported a variety of reasons why some smokers do not quit despite the well-known risks to health and other negative attributes of smoking[24]. This is an exploratory study that focused on how use of a nicotine containing e-cigarette can affect appetite (with additional assessments for smoking urges, emotion and product satisfaction) and hence doesn't account for all the potential factors that may contribute to not quitting or resumption of smoking following cessation. Furthermore, the study is an acute study (assessing appetite for 2 hours following product use - including approximate product TMax) and hence longitudinal changes following sustained product switching are not assessed. Additionally, whilst utilised broadly in associated research fields, the research methodologies have not been utilised extensively to assess e-cigarettes. Finally, study participants will be recruited from the UK population and consist of healthy adults, who smoke a minimum of 10 cigarettes a day and are aged between the 25-45 years old. As such, the data may not be reflective of populations outside these ranges.

CONCLUSION

There has been limited research on the potential physiological and psychological effects of e-cigarettes. The ability to have an effect on these domains may contribute to the acceptability of e-cigarettes to existing smokers, potentially becoming a viable alternative for smokers unwilling to stop using cigarettes due to fear of PCWG. The results of this study will be submitted for publication in a peer-reviewed scientific journal irrespective of the study findings and will not be used to

make any advertising or marketing claims relating to appetite, PCWG or any such factors. We believe that this will be a high-quality study in the field of e-cigarette research and that the findings may add to the scientific knowledge on which informed and proportionate public health policy decisions can be based.

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Conflict of interest: Olivia O'Shea, Harry Green and Nik Newland are current employees and stockholders of British American Tobacco (Investments) Ltd, which is the sponsor and funding source of this study. British American Tobacco (Investments) Ltd is the manufacturer and holder of the intellectual property rights of the investigational product used in this study
Ethical approval: Ethical approval for the study has been obtained from Wales Research Ethics Committee (Cardiff, UK; reference 20/WA/0276)

REFERENCES

1. WHO report on the global tobacco epidemic, 2021. Available at: https://www.who.int/publications/i/item/9789240032095. Accessed on 15 February 2022.
2. Murphy J, Gaca M, Lowe F, Minet E, Breheny D, Prasad K, et al. Assessing modified risk tobacco and nicotine products: Description of the scientific framework and assessment of a closed modular electronic cigarette. Regul Toxicol Pharmacol. 2017; 90:342-57.
3. Belushkin M, Tafin Djoko D, Esposito M, Korneliou A, Jeannet C, Lazzerini M, et al. Selected Harmful and Potentially Harmful Constituents Levels in Commercial e-Cigarettes. Chem Res Toxicol. 2020; 33:657-68.
4. Margham J, McAdam K, Forster M, Liu C, Wright C, Mariner D, et al. Chemical Composition of aerosol from an e-cigarette: a quantitative comparison with cigarette smoke. Chem Res Toxicol. 2016;29:1662-78.
5. Nicotine without smoke: Tobacco harm reduction. Available at: ttps://www.fda.gov/tobacco-products/health-effects-tobacco-use/nicotine-why-tobacco-products-are-addictive. Accessed on 15 February 2022.
6. McNeil A, Brose L, Calder R, Hitchman S, Hajek P and McRobbie H. E-cigarettes: an evidence update. A report commissioned by Public Health England. Public Health England. 2015;111:14-5.
7. McNeill A, Brose L, Calder R, Simonavicius E, Robson D. Vaping in England: An evidence update including vaping for smoking cessation, February 2021. Public Health England. 2021: 1-247.
8. Action on Smoking and Health. Available at: https://ash.org.uk/wp-content/uploads/2019/10/SmokingStatistics.pdf. Accessed on 15 February 2022.
9. Audrain-McGovern J, Benowitz NL. Cigarette smoking, nicotine, and body weight. Clin Pharmacol Ther. 2011;90:164-8.
10. Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. Psychopharmacology. 2010;210:453-69.
11. Schwartz A and Bellissimo N. Nicotine and energy balance: A review examining the effect of nicotine on hormonal appetite regulation and energy expenditure. Appetite. 2021;164:105260.
12. Aubin HJ, Farley A, Lycett D, Lahmek P and Aveyard P. Weight gain in smokers after quitting cigarettes: meta-analysis. BMJ. 2012;345:e4439.
13. Ashare RL, Falcone M, Lerman C. Cognitive function during nicotine withdrawal: Implications for nicotine dependence treatment. Neuropharmacology. 2014;76: 581-91.
14. Borrelli B, Mermelstein R. The role of weight concern and self-efficacy in smoking cessation and weight gain among smokers in a clinic-based cessation program. Addictive Behav. 1998;23:609-22.
15. Hughes JR. Effects of abstinence from tobacco: valid symptoms and time course. Nicotine Tob Res. 2007;9: 315-27.
16. Green HJ, O'Shea OK, Philpott HL and Newland N. An exploratory, randomised, crossover study to investigate the effect of nicotine on cognitive function in healthy adult smokers who use an electronic cigarette, after a period of smoking abstinence: study protocol. Int J Clin Trials. 2022;9:23-9.
17. Bennett LJ, Totosy de Zepetnek JO, Brett NR, Poirier K, Guo Q, Rousseau D, et al. Effect of commercially available sugar-sweetened beverages on subjective appetite and short-term food intake in girls. Nutrients. 2018;10:23-8.
18. Branton A, Akhavan T, Gladanac B, Pollard D, Welch J, Rossiter M, et al. Pre-meal video game playing and a glucose preload suppress food intake in normal weight boys. Appetite. 2014;83:256-62.
19. Yannakoulia M, Anastasiou CA, Zachari K, Sidiropoulou M, Katsaounou P and Tenta R. Acute effect of smoking and smoking abstinence on energy intake and appetite-related hormones blood concentrations. Physiol Behav. 2018;184:78-82.
20. Ebajemito JK, McEwan M, Gale N, Camacho OM, Hardie G and Proctor CJ. A randomised controlled single-centre open-label pharmacokinetic study to

examine various approaches of nicotine delivery using electronic cigarettes. Sci Rep. 2020;10:19980.
21. Perkins KA, Sexton JE, DiMarco A and Fonte C. Acute effects of tobacco smoking on hunger and eating in male and female smokers. Appetite. 1994;22:149-58.
22. Pisinger C, Jorgensen T. Weight concerns and smoking in a general population: the Inter99 study. Prev Med. 2007;44:283-9.
23. Jackson SE, Brown J, Aveyard P, Dobbie F, Uny I, West R, et al. Vaping for weight control: A cross-sectional population study in England. Addict Behav. 2019;95:211-9.
24. Guirguis AB, Ray SM, Zingone MM, Airee A, Franks AS and Keenum AJ. Smoking cessation: barriers to success and readiness to change. Tenn Med. 2010;103:45-9.

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