Brief Title: Varenicline for Nicotine Vaping Cessation in Adolescents (ViVA)

Official Title: Randomized controlled trial of varenicline for cessation of nicotine vaping in adolescent non-smokers

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Glossary

Abbreviation	Label
BID	Two times a day
BMI	Body mass index
ECDI	E-cigarette Dependence Inventory
EUC	Enhanced usual care
FDA	U.S. Food and Drug Administration
MGH	Massachusetts General Hospital
MICE	Multiple imputation via chained equations
P+BC	Placebo combined with brief behavioral counseling
TIQ	“This is Quitting” vaping cessation program
V+BC	Varenicline combined with brief behavioral counseling

Study Design

We will evaluate the efficacy of a 12-week regime of varenicline, in addition to behavioral counseling and texting support, in increasing rates of vaping cessation among nicotine dependent adolescents, compared to (a) behavioral treatment and texting support and (b) enhanced usual care and monitoring.

The study will consist of a randomized three-arm, placebo-controlled, parallel-group, double-blind clinical trial:

1. [**V+BC arm**] Participants will receive the drug varenicline, in tablet form, up to 1 mg BID for 12 weeks. Additionally, participants will (a) attend QuitVaping behavioral support sessions (completed in-person or via video-conferencing), once per week for 12 weeks, and (b) be encouraged to sign up for This Is Quitting (TIQ), a text message vaping cessation program for adolescents. We plan to assign up to 100 participants to this arm.
2. [**P+BC arm**]. Participants will receive placebo tablets, identical in appearance to varenicline, up to 1 mg BID for 12 weeks. Additionally, participants will (a) attend the QuitVaping behavioral support sessions once per week for 12 weeks, and (b) be encouraged to sign up for the TIQ program. We plan to assign up to 100 participants to this arm.
3. [**EUC arm**] Participants will be assigned to a single-blind monitoring only group and will receive no drugs nor attend behavioral support sessions. Participants will receive a brief encouragement to enroll in the TIQ program. We plan to assign up to 100 participants to this arm.

All participants will have weekly assessments to monitor vaping behavior, will receive advice to quit vaping at the first post-baseline weekly visit and be referred to the TIQ vaping cessation app. Other study-related outcomes will be assessed at the monthly visits (weeks 4, 8, 12, 16, 20, and 24).

Participants

We will recruit nicotine dependent adolescents who vape, do not smoke regularly, and are willing to try treatment to stop vaping. To do so, we plan to enroll up to 300 adolescents (and randomize as many as possible) in Greater Boston meeting these criteria. Our inclusion criteria are:

- Ages 16-25 (inclusive);
- Self-report of daily or near daily nicotine vaping for the prior ≥ 3 months, bio-verified by saliva cotinine >30 ng/ml.
- Nicotine dependence as defined by a score ≥ 4 on the 10-item E-cigarette Dependence Inventory (ECDI), and/or report persistent use despite negative consequences or prior failed quit attempts;
- Self-report of no regular combusted tobacco use in the past 2 months at enrollment and exhaled CO <10 ppm;
- Total body weight at enrollment ≥ 35 kg (77 lbs);
- Are competent and able to consent (if 18 or older), or have a parent or legal guardian who is able and willing to provide written informed consent (if under the age of 18);
- Able to understand study procedures and read and write in English;
- For participants who could become pregnant: negative urine pregnancy test at enrollment and agree to use effective contraception (e.g., abstinence, hormonal contraception, intra-uterine device, sterilization, or double barrier contraception) during the study.

Our exclusion criteria are:

- Use of a smoking cessation medication in the prior month (nicotine patch, gum, nasal spray, or inhaler, varenicline, bupropion);
- Unwilling to abstain during the study from using smoking cessation aids other than those provided by the study;
- Experienced a prior adverse drug reaction to varenicline;
- Report an unstable medical condition, epilepsy, or severe renal impairment;
- Had an inpatient psychiatric hospitalization and/or serious suicidal ideation or suicide attempt in the prior six months;
- Have active problem substance use (other than nicotine) severe enough to compromise ability to safely participate in the study protocol.
- Evidence of active problem substance use severe enough to compromise ability to safely participate, in the investigator's opinion;

- Unwilling to provide urine samples;
- Any condition or situation that would, in the investigator's opinion, make it unlikely that the participant could adhere safely to the study protocol;
- Ward of the state.

Randomization

Eligible participants will be randomly assigned in a 1:1:1 ratio, in blocks of 6, to V+BC (varenicline and behavioral counseling), P+BC (identical appearing placebo and behavioral counseling), or EUC (enhanced usual care). Randomization will be stratified by secondary or post-secondary school status. The randomization scheme will be computer generated by the Massachusetts General Hospital (MGH) Research Pharmacy by personnel with no other interactions with study staff or participants. Randomization codes will be held in the research pharmacy and made available to study investigators only in the case of urgent medical need. There will be separate randomization codes for apo-varenicline, imported from Canada under a provisional FDA allowance, and domestic generic varenicline will full FDA approval. Treatment will be assigned according to study number, assigned sequentially to eligible participants who enroll in the trial and attend the baseline visit.

Masking/Blinding

Outcome assessors, data managers, and analysts will be blinded to treatment assignments. All study staff and participants will be blind to study medication assignment for the primary outcome comparing V+BC and P+BC. Interventionists and their clinical supervisors will be unblinded to assignment to behavioral counseling and will not be involved in assessments, data management, or data analysis.

Analytic Approach

Primary Outcome

The primary outcome for the study will be…

1. Cotinine-verified self-reported nicotine vaping abstinence from week 9 to week 12 of the study.
    a. [Time frame] Self-reported abstinence and urine or saliva samples will be collected during (a) the baseline visit, (b) every week from weeks 1 to 12 during the randomization interval, and (c) at weeks 16, 20, and 24 during the follow-up interval. The primary outcome will then consist of continuous abstinence status over weeks 9, 10, 11, and 12 for each participant converted to a binary value (1 = abstinent across all 4 study visits, 0 = non-abstinent for at least one of the 4 study visits).
    b. [Biochemical verification] Self-reported nicotine vaping abstinence will be considered verified given a semi-quantitative cotinine of less than 30ng/ml. For virtual sessions, participants will provide the sample during the videoconferencing session and will show results to the assessor. Those who report no vaping use since the last study visit but who have a cotinine of 30ng/ml or higher will be considered non-abstinent. Those who are missing cotinine values but self-report vaping will be considered non-abstinent.
    c. [Self-reported abstinence] Self-reported vaping will be assessed at all visits using the timeline follow-back (TLFB; Robinson, Sobell, Sobell, & Leo, 2014). The recall period will be 60 days at enrollment and for all subsequent visits will be the interval between the prior and current visit.
    d. [Randomization groups] The primary analysis will focus on V+BC and P+BC groups.

Covariates

We will use, at a minimum, 2 covariates in our analysis and missing data imputation:

- Biological sex at birth (male [referent] versus female).
- Summed scores from the ECDI (Foulds et al., 2015), a 10-item inventory with scores ranging from 0 – 20 (higher scores indicating greater E-cigarette dependence).

All covariates will be collected during the baseline visit.

Missing Data

Missing abstinence data for any of the study weeks 9, 10, 11, or 12 will be imputed 40 times using multiple imputation via chained equations (MICE; Azur, Stuart, Frangakis, & Leaf, 2011). Abstinence status will be imputed all non-missing time points and using the set of 2 covariates collected at the baseline visit described above. Imputation will be done via fully conditional specification with predictive mean matching using logistic regression. Following each imputation iteration, the 4 observed and/or imputed values per participant across the 4 study visits will be converted into the final binary outcome via the rules given above. For instances in which a participant only partially completed the baseline ECDI, missing responses to individual questions will be singularly imputed via an item response theory model fit to all non-missing responses: a binomial regression with population-level effects for items and a participant-varying intercept term.

Statistical Model and Tests

We will use a logistic regression model to assess continuous cotinine-verified self-reported abstinence across study weeks 9 – 12 for participants in the V+BC and P+BC arms (We will exclude participants in the EUC arm). Missing data will be imputed per the method specified above. We will then apply our logistic regression model to each set of observed and imputed data, and pool the regression estimates according to Rubin's rule.

Our primary test of interest will be a dummy-coded contrast comparing the P+BC group (coded as 0) to the V+BC group (coded as 1). Statistical significance for the contrast between varenicline and placebo will be determined using a z-test applied to the pooled mean estimate divided by the pooled standard error. We hypothesize that those assigned to V+BC will have significantly higher abstinence rates compared to those assigned to P+BC, which will be confirmed with $p < 0.05$ and an odds ratio greater than one.

The logistic regression model will include the 2 covariates assessed at baseline (biological sex and summed scores for the ECDI). Covariates will be standardized (mean-centered and scaled by the standard deviation). The analysis will be intent-to-treat; all subjects randomized at the beginning of the study will be included in the analysis, irrespective of whether they receive their assigned behavioral treatment or take their assigned medication.

Secondary Outcomes

The secondary outcomes for the study will be…

1. Cotinine-verified self-reported nicotine vaping abstinence from week 9 to week 24 of the study.
    a. [Time frame] Using self-reported abstinence (see primary outcome) and biochemical verification based on urine/saliva samples (see primary outcome) collected during weeks 9, 10, 11, 12, 16, 20, and 24, the secondary outcome will consist of continuous abstinence for each participant converted to a binary value (1 = abstinent across all 7 study visits, 0 = non-abstinent for at least one of the 7 study visits).
2. Cotinine-verified self-reported nicotine vaping abstinence at week 12 of the study.
    a. [Time frame] Using self-reported abstinence (see primary outcome) and biochemical verification based on urine/saliva samples (see primary outcome) collected during week 12, the secondary outcome will consist of 7-day point-prevalence abstinence for each participant converted to a binary value (1 = abstinent over 7 days ending at week 12, 0 = otherwise).
3. Summed scores on the Minnesota Nicotine Withdrawal Scale (MNWS; Cappelleri, Bushmakin, Baker, Merikle, Olufade, & Gilbert, 2005), a 9-item inventory with scores ranging from 0 to 36 (higher scores indicate greater severity of nicotine withdrawal).
    a. [Time frame] The inventory will be administered at baseline, every week from weeks 1 – 12, and weeks 16, 20, and 24.
4. Summed scores on the Questionnaire of Vaping Craving (QVC; Dowd, Motschman, & Tiffany, 2019), a 10-item inventory with scores ranging from 10 to 70 (higher scores indicate greater cravings to vape).
    a. [Time frame] The inventory will be administered at baseline, every week from weeks 1 – 12, and weeks 16, 20, and 24.
5. Summed scores on the General Distress subscale of the Mood and Anxiety Symptoms Questionnaire (MASQ-D30; Lin, Yung, Wigman, Killackey, Baksheev, & Wardenaar, 2014).
    a. [Time frame] The inventory will be administered at enrollment, baseline and monthly during weeks 4, 8, 12, 16, 20, and 24.
6. Number of participants who report one or more adverse events as measured by the Neuropsychiatric Adverse Events Interview (NAEI; Anthenelli et al., 2016).

a. [Time frame] The interview will be conducted at enrollment, baseline, and monthly during weeks 4, 8, 12, 16, 20, and 24.

Missing Data

Missing outcome data for the 2 vaping abstinence outcomes and the 3 inventory measures will be multiply imputed.

Biochemically-Verified Vaping Abstinence

Missing abstinence data for any of the study weeks 9, 10, 11, 12, 16, 20, or 24 will be imputed 40 times using MICE via the same approach and covariates described for the primary outcome. Following each imputation iteration, for continuous abstinence over weeks 9 – 24, the 7 observed and/or imputed values per participant across the 7 study visits will be converted into the final binary outcome via the rules given above.

Inventory Measures

Missing summed scores for the MNWS, QVC, and the MASQ-D30 for any of the study weeks 1 – 24 will be imputed 40 times using MICE. Summed scores will be imputed using the set of 2 baseline covariates described above, as well as a participant's baseline summed score for the given inventory measure. Imputation will be done via fully conditional specification with predictive mean matching using linear regression.

Statistical Models and Tests

We will conduct 5 secondary analyses total for the 3 vaping abstinence outcomes, 3 secondary analyses and 3 exploratory analyses total for the 3 inventory measures, and a secondary analysis for adverse events.

Biochemically-Verified Vaping Abstinence

We will use a logistic regression model to assess (1) continuous vaping abstinence across study weeks 9 – 12, (2) continuous vaping abstinence across study weeks 9 – 24, and (3) 7-day point-prevalence cotinine-verified self-reported abstinence at week 12. Missing data will be imputed per the method specified above. We will then apply our logistic regression model to each set of observed and imputed data, and pool the regression estimates according to Rubin's rule.

The logistic regression model will include the 2 covariates assessed at baseline (biological sex and summed scores for the ECDI). Covariates will be standardized (mean-centered and scaled by the standard deviation). The analysis will be intent-to-treat; all subjects randomized at the beginning of the study will be included in the analysis, irrespective of whether they receive their assigned behavioral treatment or take their assigned medication.

We will conduct two types of analyses:

1. We will assess a single dummy-coded contrast comparing the P+BC group (coded as 0) to the V+BC group (coded as 1), excluding participants in the EUC group. Statistical significance will be determined using a z-test applied to the pooled mean estimate divided by the pooled standard error. We will conduct this analysis for our two secondary vaping abstinence outcomes.
2. We will assess a pair of dummy-coded contrasts comparing the EUC group (coded as 0) against (1) the V+BC group (coded as 1) and (2) the P+BC group (coded as 1). Statistical significance will be determined via an analysis of variance comparing a simpler null model (with contrasts for V+BC and P+BC fixed to zero) against the more complex model with both contrasts freely estimated. If the Wald test for the model comparison is significant, we will conduct post-hoc tests assessing the 3 possible comparisons between groups (EUC vs. P+BC, EUC vs. V+BC, and P+BC vs. V+BC). We will conduct this analysis for our primary vaping abstinence outcome as well as our two secondary vaping abstinence outcomes.

Table 1 summarizes all secondary analyses for the vaping abstinence outcomes. Tests will be deemed statistically significant for $p < 0.05$ following a correction using the Benjamini-Hochberg method across the 5 analyses.

Table 1: Secondary analyses for vaping abstinence outcomes

Vaping abstinence outcome	Contrast
Continuous abstinence (over weeks 9 – 12)	Omnibus test for EUC vs. V+BC, EUC vs. P+BC, and P+BC vs. V+BC
Continuous abstinence (over weeks 9 – 24)	Contrast of P+BC vs. V+BC (No EUC) Omnibus test for EUC vs. V+BC, EUC vs. P+BC, and P+BC vs. V+BC
Point-prevalence abstinence (week 12)	Contrast of P+BC vs. V+BC (No EUC) Omnibus test for EUC vs. V+BC, EUC vs. P+BC, and P+BC vs. V+BC

Inventory Measures

We will use a linear regression model to assess the post-baseline summed scores collected over weeks 1 – 12 (at weekly or monthly intervals) for (1) the MNWS, (2) the QVC, and (3) the MASQ-D30. The linear model will be estimated using generalized estimating equations (GEE; Liang & Zeger, 1986),

providing estimates and standard errors robust to violations of distributional assumptions (e.g., normality) and heteroscedasticity.

The linear regression model will include covariates for (a) biological sex and baseline summed scores for the ECDI (see above), (b) a participant's baseline score on the given inventory measure, and (c) linear and quadratic time trend terms using number of days since the baseline visit. Covariates will be standardized (mean-centered and scaled by the standard deviation). The analysis will be intent-to-treat; all subjects randomized at the beginning of the study will be included in the analysis, irrespective of whether they receive their assigned behavioral treatment or take their assigned medication.

We will conduct two types of analyses:

3. We will assess a single dummy-coded contrast comparing the P+BC group (coded as 0) to the V+BC group (coded as 1), excluding participants in the EUC group. Statistical significance will be determined using a z-test applied to the pooled mean estimate divided by the pooled standard error. This will be a secondary analysis.
4. We will assess a pair of dummy-coded contrasts comparing the EUC group (coded as 0) against (1) the V+BC group (coded as 1) and (2) the P+BC group (coded as 1). Statistical significance will be determined via an analysis of variance comparing a simpler null model (with contrasts for V+BC and P+BC fixed to zero) against the more complex model with both contrasts freely estimated. If the Wald test for the model comparison is significant, we will conduct post-hoc tests assessing the 3 possible comparisons between groups (EUC vs. P+BC, EUC vs. V+BC, and P+BC vs. V+BC). This will be an exploratory analysis.

Table 2 summarizes all secondary and exploratory analyses for the inventory measures. Tests will be deemed statistically significant for $p < 0.05$ following a correction using the Benjamini-Hochberg method across the 3 secondary analyses and 3 exploratory analyses, respectively.

Table 2: Secondary and exploratory analyses for inventory measures

Inventory measure	Contrast	Exploratory
MNWS	Contrast of P+BC vs. V+BC (No EUC)	
	Omnibus test for EUC vs. V+BC, EUC vs. P+BC, and P+BC vs. V+BC	Yes
QVC	Contrast of P+BC vs. V+BC (No EUC)	
	Omnibus test for EUC vs. V+BC, EUC vs. P+BC, and P+BC vs. V+BC	Yes
MASQ-D30	Contrast of P+BC vs. V+BC (No EUC)	
	Omnibus test for EUC vs. V+BC, EUC vs. P+BC, and P+BC vs. V+BC	Yes

Adverse events

We will tally the number participants who report one or more adverse events during the NAEI interview across weeks 4, 8, and 12, looking specifically at the 2 x 2 contingency tables for (a) the P+BC group versus V+BC group, and (b) the EUC group versus the V+BC group. We will then assess whether the number of participants reporting one or more adverse events differs between the two groups using Fisher's exact test. Differences between groups will be deemed statistically significant for $p < 0.025$.

Sensitivity Analyses

Across our primary and secondary analyses, at a minimum we will conduct the following sensitivity analyses:

1. We will test whether our conclusion on efficacy is robust to the inclusion/exclusion of the two covariates (biological sex and nicotine dependence severity). We will rerun analyses excluding these covariates and see if conclusions change.
2. We will test whether our conclusion on efficacy is robust to the approach for imputation of missing data. We will (a) rerun the adjusted (i.e., with covariates) models on the observed data only and (b) rerun the adjusted models on a dataset with the observed data and all missing outcome data imputed as non-abstinent.
3. We will conduct a per protocol analysis by evaluating results among participants who use varenicline on most days in the trial (e.g., > 50 or 75%).

Power

Sample size was determined based on the assumption that use of varenicline for vaping cessation in adolescents would require an effect that at least doubled cessation rates over placebo to be worth the risks inherent in use of pharmacotherapy. Abstinence rates of 24% have been reported with TIQ alone in adolescents who vaped and were not necessarily dependent (Graham, Jacobs, & Amato, 2020; Graham, Amato, Cha, Jacobs, Bottcher, & Papandonatos, 2021). In this trial, requiring nicotine dependence to enroll, we postulate that addition of varenicline to behavioral counseling and TIQ will double abstinence rates. A sample size of 100 per arm, with 80 analyzable per arm, would yield power of 0.88 with a two-sided alpha of 0.05 with abstinence rates of 25% in the P+BC arm and 50% in the V+BC arm.

Software and Data Management

All analyses will be done using the statistical software R (version 4.1.1; R Core Team, 2021) and integrated development environment RStudio (version 2020.9.0.351; RStudio Team, 2021). Data will be prepared using the R packages 'dplyr' (version 1.0.7; Wickham, François, Henry, & Müller, 2021) and 'tidyr' (version 1.1.4; Wickham, 2021). Models will be fit using the R package 'geepack' (version 1.3-2; Højsgaard, Halekoh, & Yan, 2006). Missing data will be imputed using the R package 'mice' (version 3.13.0; Van Buuren & Groothuis-Oudshoorn, 2011). Reproducible code and de-identified data will be organized using the R package 'targets' (version 0.8.1; Landau, 2021).

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