

Varenicline for Youth Nicotine Vaping Cessation

A Randomized Clinical Trial

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IMPORTANCE Electronic cigarette use (vaping) among adolescents and young adults is common. Few treatments have been tested in this population.

OBJECTIVE To evaluate the efficacy of varenicline for nicotine vaping cessation in youth who do not smoke tobacco regularly.

DESIGN, SETTING, AND PARTICIPANTS A 3-group randomized clinical trial compared 12 weeks of double-blind varenicline vs placebo, each added to brief, remotely delivered behavioral counseling and compared with single-blind enhanced usual care, with monthly follow-up to 24 weeks. The trial was conducted among youth, aged 16 to 25 years, who vaped nicotine daily or near daily, did not regularly smoke tobacco, and wanted to reduce or quit vaping, in a single US state from June 2022 to May 2024. Data collection ended May 28, 2024.

INTERVENTIONS Participants were randomized (1:1:1) to 12 weeks of varenicline titrated to 1 mg twice daily over 7 days (standard titration), weekly counseling, and referral to text messaging vaping cessation support (This is Quitting [TIQ]) (n = 88); identical placebo, weekly counseling, and referral to TIQ (n = 87); or enhanced usual care (referral to TIQ only) (n = 86).

MAIN OUTCOMES AND MEASURES Biochemically verified continuous vaping abstinence for the last 4 weeks of varenicline treatment vs placebo (primary outcome). Secondary outcomes included bioverified continuous abstinence from weeks 9 through 24 in the varenicline and placebo groups. Additional analyses compared varenicline group and placebo group with enhanced usual care.

RESULTS Of 261 randomized participants (mean age, 21.4 years; 53% female), 254 completed the trial (97.3%). For varenicline and placebo, continuous abstinence rates were 51% vs 14% during weeks 9 through 12 (adjusted odds ratio [aOR], 6.5 [95% CI, 3.0-14.1]; $P < .001$) and 28% vs 7% during weeks 9 through 24 (aOR, 6.0 [95% CI, 2.1-16.9]; $P < .001$). Varenicline had higher continuous abstinence rates vs enhanced usual care during weeks 9 through 12 (51% vs 6%; aOR, 16.9 [95% CI, 6.2-46.3]) and during weeks 9 through 24 (28% vs 4%; aOR, 11.0 [95% CI, 3.1-38.8]). Continuous abstinence rates were not significantly different between the placebo and enhanced usual care groups. Study medication was generally well tolerated. Two varenicline participants (2%) and 1 placebo participant (1%) discontinued study medications due to adverse events. No drug-related serious adverse events occurred. Treatment-emergent adverse events were reported by 76 (86%) in the varenicline group, 68 (79%) in the placebo group, and 68 (79%) in the enhanced usual care group.

CONCLUSIONS AND RELEVANCE Varenicline, combined with behavioral counseling, increased vaping abstinence in youth who vape nicotine and do not regularly smoke tobacco.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: [NCT05367492](https://clinicaltrials.gov/ct2/show/study/NCT05367492)

JAMA. 2025;333(21):1876-1886. doi:[10.1001/jama.2025.3810](https://doi.org/10.1001/jama.2025.3810)
Published online April 23, 2025.

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Electronic cigarettes (e-cigarettes) are the most used nicotine-containing product among youth, with use in the past 30 days reported by 7.8% of high school students in 2024¹ and by 24.1% of those aged 18 to 25 years in 2023.² E-cigarette use is most prevalent among the 18- to 25-year-old age group.² The proportion of those aged 16 to 25 years who vape and have never regularly smoked is increasing.^{1,3} In 2021, 71.5% of those aged 18 to 20 years and 53% of those aged 21 to 24 years who reported current e-cigarette use reported never using combustible cigarettes.⁴ Nearly half of those aged 18 to 24 years who use e-cigarettes do so daily⁴; the high prevalence of e-cigarette use puts youth at risk for nicotine addiction,⁵ uptake of combusted tobacco and other substance use,⁶⁻⁸ and direct negative health effects of vapor exposure such as carcinogen and heavy metal exposure and pulmonary inflammation.⁹⁻¹¹

To our knowledge, no pharmacotherapy trials have been conducted for cessation of vaped nicotine in youth, despite recent surveys indicating that more than one-half of youth who vape nicotine want to quit or reduce use.¹² Effective interventions are critical to aid the estimated 1.63 million US youth who currently use e-cigarettes regularly.¹³ Varenicline is a partial $\alpha 4\beta 2$ nicotinic acetylcholine receptor agonist that has been well tolerated in youth, has demonstrated mixed effects for smoking cessation in youth, and has preliminary evidence for efficacy for vaping cessation in adults.¹¹⁻¹⁴

This study tested the hypothesis that youth assigned to varenicline and behavioral counseling would have higher continuous vaping abstinence rates than those assigned to placebo and behavioral counseling. All participants received referral to This is Quitting (TIQ; Truth Initiative), a free text messaging-based program that provides support for vaping cessation for adolescents and young adults.¹⁴ To explore the effectiveness of behavioral counseling for vaping cessation in this population, this study included a single-blind comparison group that received TIQ referral only (enhanced usual care).

Methods

Trial Design

This 3-group randomized clinical trial was approved by the Mass General Brigham institutional review board and overseen by a data and safety monitoring board. Participants provided written informed consent and were enrolled from June 2022 to November 2023. Data collection ended May 28, 2024. The trial was registered on ClinicalTrials.gov (NCT05367492).¹⁵ Supplementary materials include the protocol and statistical analysis plan (Supplement 1).¹⁵ Results are reported following CONSORT and EQUATOR guidelines.

Setting and Participants

The trial recruited participants from a single US state. Individuals were eligible to enroll if they were aged 16 to 25 years; self-reported nicotine vaping 5 or more days per week in the prior 90 days¹⁶; had interest in quitting or reducing nicotine vaping in the next month and no prior regular tobacco smoking, defined as smoking 5 or more days per week; exhibited nicotine dependence (score ≥ 4 on the 10-item E-cigarette De-

Key Points

Question Is varenicline, when added to brief, remotely delivered behavioral support, efficacious and well tolerated for nicotine vaping cessation in youth?

Findings In this 12-week randomized clinical trial in 261 treatment-seeking youth, aged 16 to 25 years, continuous abstinence rates in the last month of treatment (51% vs 14%) and at 6-month follow-up (28% vs 7%) were higher in the varenicline group than in the placebo group. Treatment-emergent adverse events did not differ significantly between groups.

Meaning Varenicline, when added to brief cessation counseling, is well tolerated and promotes nicotine vaping cessation compared with placebo in youth with addiction to vaped nicotine.

pendence Inventory [ECIDI])¹⁷; had a saliva cotinine level greater than 30 ng/mL (827.64 nmol/L); and had an expired carbon monoxide level less than 10 ppm to exclude current tobacco smoking. Exclusion criteria included smoking cessation pharmacotherapy use in the prior month, inpatient psychiatric hospitalization, suicide attempt, or other unstable medical condition in the prior 6 months. See the eProtocol in Supplement 1.

Recruitment, Enrollment, Randomization, Masking, Retention

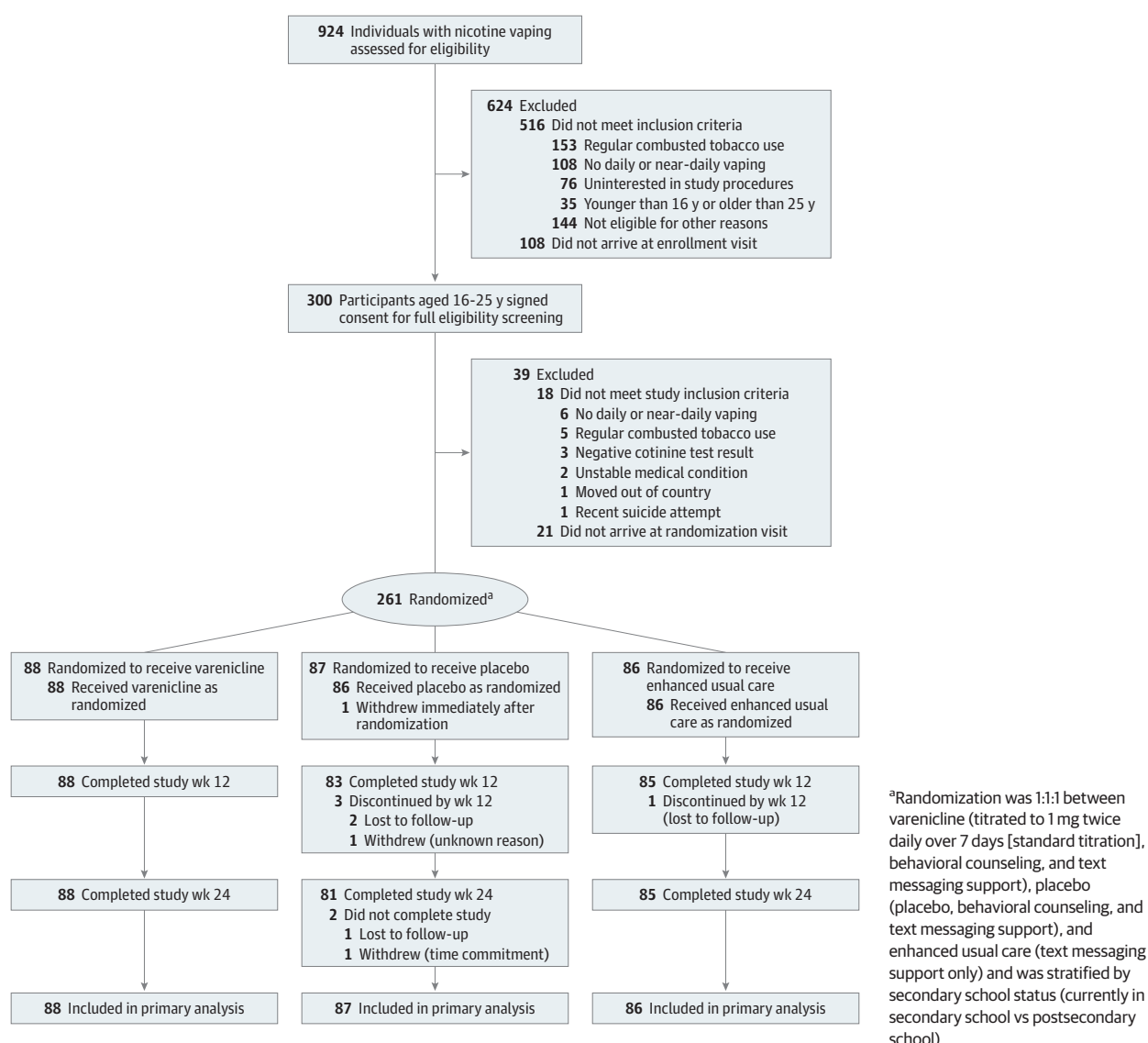
Participants were recruited through social media and public transportation advertising. Eligibility was assessed via telephone screen, and participants provided written informed consent or assent with parental consent for participants younger than 18 years. Massachusetts General Hospital research pharmacy staff not associated with the study produced computer-generated code to individually randomize enrolled participants in a 1:1:1 ratio in blocks of 6 to varenicline plus behavioral counseling, placebo plus behavioral counseling, or enhanced usual care (Figure 1), stratified by status as currently in secondary school vs postsecondary school. All study staff were blind to study medication allocation. Behavioral counselors were not involved in assessments, data management, or analysis. To optimize retention and adherence, participants received financial compensation up to \$570 for completing assessments, and those assigned to varenicline plus behavioral counseling and to placebo plus behavioral counseling were incentivized \$1 for each uploaded smartphone app video recording of medication self-administration (Scene Health) that also texted reminders to take study medication.

Interventions

Pharmacotherapy (Varenicline or Placebo) and Behavioral Counseling Participants randomized to pharmacotherapy received 12 weeks of varenicline titrated to 1 mg twice daily over 7 days (standard titration), or identical-appearing placebo, matched through overencapsulation to ensure blinding. Study medication was dispensed at baseline, week 2, and week 4. Adherence was confirmed via pill counts and medication self-administration video-recorded by participants.

Participants assigned to pharmacotherapy received 12 weekly 20-minute behavioral counseling sessions provided by a lay counselor trained in a manualized cognitive behavioral

Figure 1. Screening, Randomization, and Follow-Up of Trial Participants in the Study of Varenicline Added to Behavioral Treatment and Text Messaging Support for Vaping Cessation in Youth



intervention developed to support vaping cessation in youth.¹⁵ Participants were encouraged to set a quit date prior to their week 3 counseling session. See [Supplement 2](#) for the eManual and training and fidelity assessments. Average number of sessions attended was calculated as a measure of participant adherence to behavioral counseling.

Enhanced Usual Care

All study participants received a TIQ referral. TIQ use was assessed by self-report at each assessment. Participants randomized to enhanced usual care, a minimal care control, received no additional intervention.

Measures

Assessments were performed at enrollment, randomization, weekly for 12 weeks, and at weeks 16, 20, and 24 by study staff blind to treatment allocation. Visits were conducted virtually

via Zoom, when needed, to maximize data acquisition. Participants were encouraged to complete all assessments regardless of vaping status or intervention uptake. Information collected at enrollment included self-reported age, sex, race, ethnicity, and medical history. Nicotine vaping, tobacco smoking, and other drug use was assessed using timeline follow-back methods. Severity of nicotine dependence was assessed with the ECDI. Self-report of vaping since the last visit and saliva cotinine concentration to confirm self-reported abstinence were conducted at every study visit. For visits performed virtually, saliva cotinine collection kits and instructions were mailed in advance, allowing participants to produce and test the saliva sample in view of the assessor via videoconference.¹⁸

Outcomes

The primary outcome was biochemically confirmed continuous nicotine vaping abstinence across study weeks 9 through

12. Verified abstinence at each visit required self-report of no electronic cigarette use since the last visit and observed cotinine level of 30 ng/mL (827.64 nmol/L) or less¹⁹ using the iScreen Oral Fluid Test, a lateral flow chromatographic immunoassay for qualitative detection of cotinine in oral fluids, with a cutoff concentration of 30 ng/mL.¹⁹ Secondary abstinence outcomes included bioverified continuous abstinence from study weeks 9 to 24 and 7-day point prevalence abstinence at week 12.

To assess nicotine withdrawal symptoms, craving, and negative mood, secondary outcomes were Minnesota Nicotine Withdrawal Scale^{20,21} and Questionnaire of Vaping Craving²² scores assessed weekly over 12 weeks and Mood and Anxiety Symptoms Questionnaire (30-item)^{23,24} General Distress scores assessed monthly.

Safety outcomes included treatment discontinuation due to adverse events; incidence of treatment-emergent adverse events during the 24-week study period, assessed using open-ended questioning and the Neuropsychiatric Adverse Event Inventory (NAEI)²⁵ during the 12-week treatment period; and initiation of regular tobacco smoking.

Sample Size

Sample size was determined to power the primary comparison, based on the assumption that use of varenicline for vaping cessation in adolescents would require an effect that at least doubled abstinence rates over placebo to justify any risks inherent in use of pharmacotherapy in youth. A vaping abstinence rate of 24.1% had been reported with TIQ alone in adolescents.²⁶ Postulating that adding varenicline to behavioral counseling and TIQ would double abstinence rates, a sample of 100 per group, with 80 analyzable per group, would yield power of 0.88 with a 2-sided α of .05 for abstinence rates of 50% in the varenicline plus behavioral counseling group and 25% in the placebo plus behavioral counseling group.

Statistical Analysis

The primary analysis was logistic regression comparing varenicline plus behavioral counseling group vs placebo plus behavioral counseling, excluding enhanced usual care data, reporting a Wald test of the odds ratio adjusting for biological sex and baseline ECDI score. As a secondary analysis, we fit another logistic regression model including all 3 study groups using a dummy-coded categorical variable for study group, adjusting for the same covariates. From this model we performed an omnibus Wald test for differences between the study groups and, if significant at $P < .05$, reported exploratory pairwise adjusted odds ratios between groups from this model. Post hoc analyses report unadjusted estimates of pairwise risk differences between varenicline plus behavioral counseling, placebo plus behavioral counseling, and enhanced usual care with 95% confidence intervals. Additional post hoc analyses include the primary outcome stratified by sex and by age.

We performed the same analyses for the secondary abstinence outcomes, continuous week 9 through 24 abstinence and 7-day abstinence at week 12. P values for secondary comparisons were adjusted for multiplicity using the Benjamini-Hochberg method with a false discovery rate of .05²⁷ for 3 families

of tests: (1) the secondary comparisons of abstinence outcomes and, as described below, (2) the varenicline vs placebo comparisons of inventory outcomes (eg, the Minnesota Nicotine Withdrawal Scale), and (3) the omnibus tests across all 3 groups for the inventory outcomes (eTable 1 in Supplement 2).

Analyses included participants based on their assigned group in an intent-to-treat interpretation. For the primary comparison of the primary outcome, a per-protocol analysis was also performed among those at least 80% adherent to both medication and the behavioral intervention, using inverse probability weighting to correct for differences in adherence²⁸ (eTable 2 in Supplement 2). While the statistical analysis plan was to adjust analyses for secondary vs postsecondary school status, this was omitted because nearly all participants were postsecondary school.

Our primary and secondary analyses of abstinence outcomes required abstinence confirmation with measurement of cotinine level, with abstinence considered missing if cotinine verification was missing; missing abstinence was addressed using multiple imputation by chained equations performed separately for each group, incorporating covariates of sex, baseline ECDI score, and 7-day point prevalence abstinence at each assessment. We report missingness sensitivity analyses using alternative approaches including complete case analyses and reclassification of missing self-report or cotinine verification as nonabstinence (eTable 2 in Supplement 2). Observed 7-day point prevalence abstinence rates at each study visit using nonmissing data only are reported by group.

Continuous secondary outcomes were analyzed as repeated measures. For each outcome we report the adjusted mean difference comparing varenicline plus behavioral counseling vs placebo plus behavioral counseling excluding enhanced usual care data, using generalized estimating equations with a working AR(1) correlation matrix, adjusting for sex, baseline ECDI score, baseline outcome score, and a quadratic trend of time. Next, we fit models with the same covariates to all study groups using a dummy-coded categorical variable for study group and performed omnibus Wald tests to assess differences by group. If this test was significant at $P < .05$, we reported pairwise adjusted mean differences from this model between groups. Missingness in repeated measures was handled using multiple imputation including the model covariates; sensitivity analyses restricted to complete cases are reported (eTable 2 in Supplement 2). For each outcome we report unadjusted descriptive means and 95% confidence intervals at each visit using observed data only.

Adverse events are reported by group. Statistical analyses were performed using the R version 4.2.2 (R Foundation), the mice package for multiple imputation, and the geepack package for generalized estimating equations models.

Results

Participants

Of 300 youth who passed initial eligibility screening and consented to enroll, 261 met eligibility requirements and were randomized to varenicline plus behavioral counseling ($n = 88$),

placebo plus behavioral counseling ($n = 87$), or enhanced usual care ($n = 86$) (Figure 1). Primary efficacy analyses included all 261 randomized participants. Safety analyses included 260 participants who attended 1 or more postbaseline study visits. Participants were comparable on baseline characteristics (Table 1).²⁹⁻³¹ Eight percent of participants reported any combusted tobacco use in the 90 days before randomization, 71.6% reported any prior 30-day cannabis use, and 95.0% reported any prior 30-day alcohol use (Table 1).

Overall, 254 participants completed the 24-week trial (97.3% of those randomized). Study drug adherence assessed with pill counts indicated that 120.2 (SD, 45.4) pills were taken of 165 possible by varenicline plus behavioral counseling participants (72.8% [SD, 27.5%]) and 104.8 (SD, 58.8) by placebo plus behavioral counseling participants (63.5% [SD, 35.6%]). Video evidence of medication adherence was provided for 85.9 (SD, 54.4) (52.1% [SD, 33.0%]) of possible varenicline doses and 69.1 (SD, 56.4) (41.9% [SD, 34.2%]) of possible placebo doses. Behavioral counseling attendance was 10.1 (SD, 3.3) of 12 sessions (83.8% [SD, 27.6%]) in the varenicline plus behavioral counseling group and 7.9 (SD, 4.7) (65.8% [SD, 39.6%]) in the placebo plus behavioral counseling group, with 80% or more of counseling sessions attended by 78.4% (69/88) of those assigned to varenicline plus behavioral counseling and 59.8% (52/87) of those assigned to placebo plus behavioral counseling. Behavioral counselor fidelity ratings are presented in eTables 3A and 3B in Supplement 2.

Enrollment in TIQ was 41% (36/88) among participants in the varenicline plus behavioral control group, 36% (31/87) in the placebo plus behavioral control group, and 74% (64/86) in the enhanced usual care group. Engagement with TIQ was a median days per week reading texts of 0 (IQR, 0-0.8) in the varenicline plus behavioral control group, 0 (IQR, 0-1.7) in the placebo plus behavioral control group, and 1.8 (IQR, 0.1-3.5) in the enhanced usual care group and a median days per week interacting with texts of 0 (IQR, 0-0.1) in the varenicline plus behavioral control group, 0 (IQR, 0-0.2) in the placebo plus behavioral control group, and 0 (IQR, 0-0.65) in the enhanced usual care group (see eTable 4 in Supplement 2 for TIQ interaction details).

Efficacy

In analyses restricted to the varenicline plus behavioral counseling and placebo plus behavioral counseling groups, bioverified continuous abstinence rates for the varenicline plus behavioral counseling and placebo plus behavioral counseling groups were 51% vs 14% over the last 4 weeks of treatment (weeks 9-12, primary outcome) (adjusted odds ratio [aOR], 6.5 [95% CI, 3.0-14.1]; $P < .001$) and 28% vs 7% over weeks 9 through 24 (aOR, 6.0 [95% CI, 2.1-16.9]; $P = .001$) (Table 2). The primary outcome stratified by sex and by age is presented in eTable 5 in Supplement 2 and by remote bioverification in eTable 6 in Supplement 2.

Prespecified omnibus tests of each abstinence outcome showed significant differences. In exploratory analyses fit to the full data, those in the varenicline plus behavioral counseling group had higher continuous abstinence rates than those

in the enhanced usual care group over weeks 9 through 12 (51% vs 6%; aOR, 16.9 [95% CI, 6.2-46.3]) and over weeks 9 through 24 (28% vs 4%; aOR, 11.0 [95% CI, 3.1-38.2]). Placebo plus behavioral counseling did not provide statistically significant benefit over enhanced usual care in continuous abstinence over weeks 9 through 12 (14% vs 6%; aOR, 2.6 [95% CI, 0.9-7.9]) or weeks 9 through 24 (7% vs 4%; aOR, 2.0 [95% CI, 0.5-8.5]) (Table 2).

Withdrawal, Craving, and General Distress

In analyses restricted to varenicline plus behavioral counseling and placebo plus behavioral counseling, those assigned to varenicline plus behavioral counseling compared with placebo plus behavioral counseling had lower average ratings longitudinally of nicotine withdrawal severity assessed using the Minnesota Nicotine Withdrawal Scale (β [average mean difference in the scale scores], -1.88 [95% CI, -2.93 to -0.83]; $P = .001$), craving assessed using the Questionnaire of Vaping Craving (β , -6.76 [95% CI, -9.08 to -4.45]; $P < .001$), and general distress assessed using the Mood and Anxiety Symptoms Questionnaire (β , -1.78 [95% CI, -3.08 to -0.48]; $P = .008$). Omnibus tests using all 3 study groups showed statistically significant differences in means across the 3 groups for all 3 measures (Figure 2B-D; eTable 7 in Supplement 2).

Safety

Treatment-emergent adverse events were similar between the varenicline plus behavioral counseling and placebo plus behavioral counseling groups, as assessed by open-ended questioning (any adverse events, 76 [86%] for varenicline plus behavioral counseling vs 68 [79%] for placebo plus behavioral counseling) and with the NAEI (71 [81%] for varenicline plus behavioral counseling vs 61 [71%] for placebo plus behavioral counseling) ($P = .16$). Adverse event rates in the varenicline group were similar to prior reports, with rates of nausea (58%), vivid dreams (39%), and insomnia (31%) higher in participants assigned to varenicline than placebo. Study medication was discontinued by 3 (2%) and dose reduced by 5 (3%) participants due to an adverse event. No participants who were abstinent from nicotine vaping at week 24 reported any past-month tobacco smoking. Progression to regular tobacco smoking (≥ 5 of 7 days in the past month) by week 24 was reported in 5 participants (2%), none of whom were abstinent from nicotine vaping at week 24 (Table 3).

Discussion

This double-blind, placebo-controlled, randomized clinical trial tested the efficacy and safety of varenicline, combined with behavioral counseling and TIQ referral, to aid nicotine vaping cessation in youth who used e-cigarettes daily or near daily, did not smoke tobacco regularly, and wished to reduce or quit vaping. Varenicline increased the proportion of participants achieving bioverified 4-week continuous vaping abstinence at the end of treatment (51% vs 14%). Secondary abstinence outcomes, including higher rates of continuous abstinence at 24 weeks in the varenicline vs the placebo groups, support the

Table 1. Baseline Characteristics of Study Participants by Intervention Group

Measure	Varenicline (n = 88)	Placebo (n = 87)	Enhanced usual care (n = 86)
Age, mean (SD), y	21.6 (2)	21.4 (2.1)	21.4 (2)
Sex, No. (%)			
Female	46 (53)	47 (54)	46 (54)
Male	42 (48)	40 (46)	40 (46)
Race, No. (%) ^a			
Asian	13 (15)	17 (20)	18 (21)
Black	5 (6)	7 (8)	4 (5)
Multiracial	10 (11)	10 (12)	8 (9)
White	56 (64)	47 (54)	55 (64)
Other ^b	4 (5)	6 (7)	1 (1)
Hispanic or Latino(a) ethnicity, No. (%) ^a	17 (19)	18 (21)	8 (9)
Postsecondary school, No. (%)	86 (98)	85 (98)	86 (100)
Nicotine use			
E-cigarette use			
Average days used per week in last 30 d, median (IQR)	7 (7-7)	7 (7-7)	7 (7-7)
E-cigarette Dependence Inventory, mean (SD) ^c	12.5 (3.8)	13.7 (4)	12.8 (3.8)
Motivation to quit vaping, mean (SD) ^d	7.1 (1.7)	6.7 (1.8)	7.1 (1.6)
Minnesota Nicotine Withdrawal Scale total score, mean (SD) ^e	10.5 (6.1)	10.6 (6.1)	11.2 (6.0)
Questionnaire of Vaping Craving total score, mean (SD) ^f	41.3 (11.5)	42.3 (13.1)	38.5 (13.8)
Combusted tobacco use			
Any use in last 30 d, No. (%)	6 (7)	7 (8)	8 (9)
Average days used per week in last 30 d, median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)
Smoked ≥100 cigarettes lifetime, No. (%)	9 (10)	7 (8)	5 (6)
Other substance use			
Cannabis use			
Any use in last 30 d, No. (%)	61 (69)	64 (74)	62 (72)
Average days used per week in last 30 d, median (IQR)	0.9 (0-4.3)	2.1 (0-5.1)	1.2 (0-4.8)
Cannabis Use Disorders Identification Test-Revised, median (IQR) ^g	6 (2-11.5)	8 (3-14)	8 (3-14)
Alcohol use			
Any use in last 30 d, No. (%)	87 (99)	79 (91)	82 (95)
Average days used per week in last 30 d, median (IQR)	1.4 (0.7-2)	1.2 (0.5-1.9)	0.9 (0.5-1.9)
Alcohol Use Disorders Identification Test, median (IQR) ^h	5 (3-9)	7 (4-9)	6 (4-10)
Any self-reported psychiatric diagnosis, No. (%)	60 (68)	61 (70)	55 (64)
Current psychotropic medication use, No. (%)	33 (38)	33 (38)	33 (38)
MASQ Total Score, mean (SD) ⁱ	57.8 (14.5)	58.3 (14.8)	58.6 (15.3)
MASQ General Distress Score, mean (SD)	17.4 (6.7)	17.5 (6)	18.8 (7.9)

^a Race and ethnicity were assessed by participants' response to a fixed-category question.

^b Races in the other category include 1 American Indian/Alaska Native participant and 2 Middle Eastern/North African participants (grouped together due to small sample sizes), 7 Hispanic/Latino participants who listed Hispanic as both their race and ethnicity, and 1 participant who chose not to disclose race.

^c As measured by the Penn State Electronic Cigarette Dependence Index (ECDI), a 10-item scale with a range of scores from 0 to 20. Higher scores indicate greater dependence (not dependent [score 0-3], 0 participants; low dependence [score 4-8], 42 participants; medium dependence [score 9-12], 62 participants; high dependence, [score ≥13], 157 participants).

^d Motivation to quit was assessed by a single-item scale from the PhenX Toolkit,²⁹ with scores from 1 to 10 (not at all to very much).

^e An 8-item assessment of nicotine withdrawal symptoms reported on an ordinal scale from 0 (not at all) to 4 (extreme), with total scores ranging from 0 to 32.

^f A 10-item measure of desire and intent to vape and anticipation of positive outcomes from vaping. Each item is scored on a 7-point Likert scale from 1 (strongly disagree) to 7 (strongly agree), with total scores ranging from 10 to 70.

^g A screening tool designed to assess problematic cannabis use³⁰; consists of 8 self-report items that measure frequency of use, symptoms of dependence,

and the negative impacts of cannabis on daily life over the past 6 months.

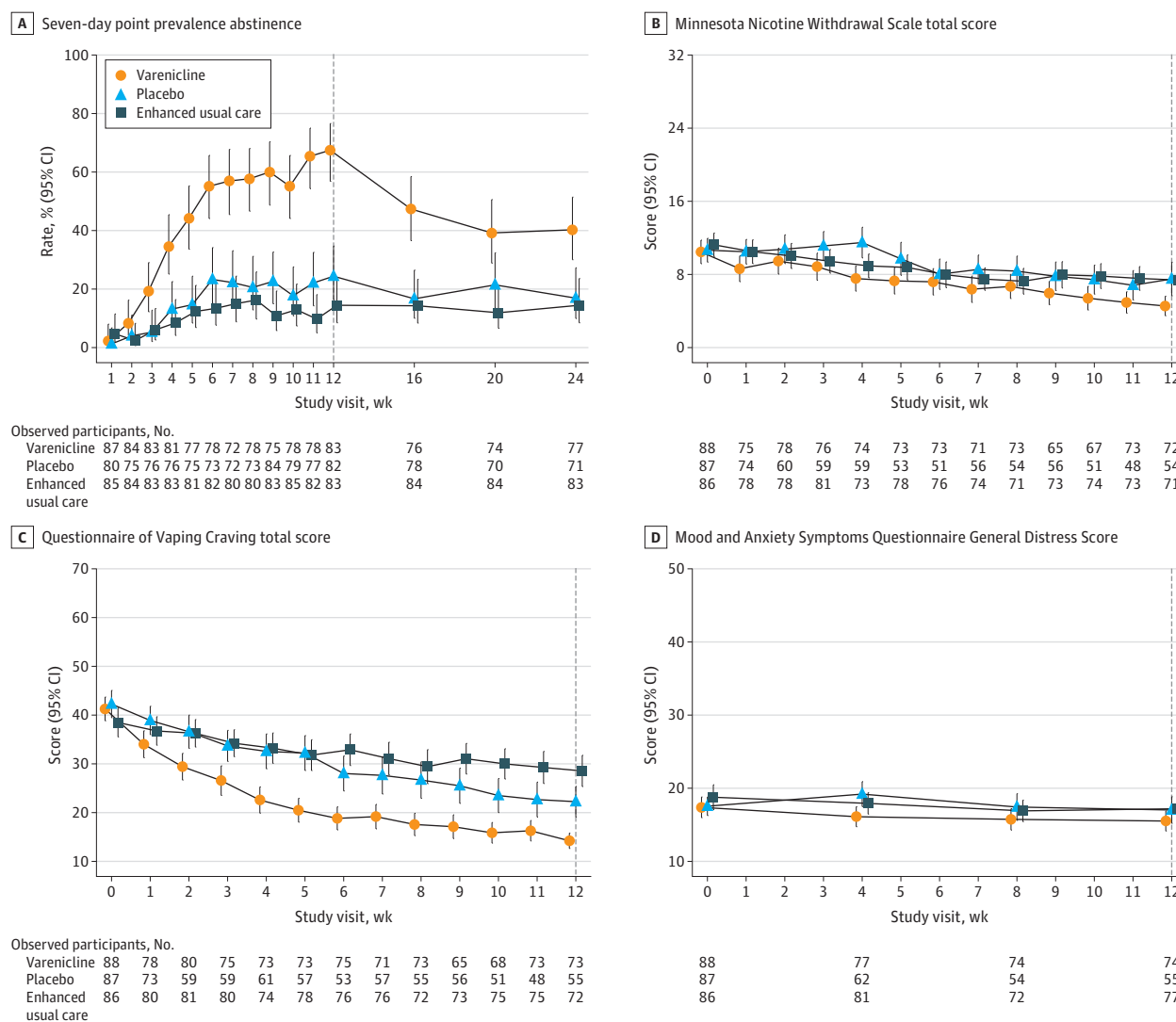
Each item scored on a scale from 0 to 4, with higher scores indicating greater severity of cannabis-related problems. The total score can range from 0 to 32, and a score of 8 or more typically suggests a potential cannabis use disorder.

^h A 10-item screening tool with scores from 0 to 40, with higher scores indicating greater likelihood that alcohol use is negatively affecting health, with scores of 8 to 14 indicating likely harmful/hazardous drinking and 15 or greater indicating likely alcohol use disorder.³¹

ⁱ A 30-item adaptation of the original 96-item Mood and Anxiety Symptoms Questionnaire (MASQ), which instructs participants to rate how often in the past week they have experienced symptoms of depression and anxiety on a 5-point Likert scale from 1 (not at all) to 5 (extremely). Symptoms are organized into three 10-item subscales: negative affect (eg, "Felt pessimistic about the future"), positive affect (eg, "Felt really happy"), and somatic arousal (eg, "Heart was racing or pounding"). Positive-affect items are reverse-scored, then a sum is calculated to reflect overall degree of mood and anxiety symptoms, with higher scores indicating more mood and anxiety symptoms. The 30-item adaptation has demonstrated good internal consistency and construct validity, commensurate to that of the full MASQ. It has been validated for use in adolescent and young adult community samples.²⁴

Table 2. Biochemically Confirmed E-Cigarette Abstinence by Treatment Group

Outcome measure	No. (%) ^a		Comparisons including all 3 study groups			
	Varenicline (n = 88)	Placebo (n = 87)	Enhanced usual care (n = 86)	Unadjusted risk difference, % (95% CI) ^b	aOR (95% CI) ^c	P value for aOR ^c
Comparisons excluding enhanced usual care group, varenicline vs placebo						
Primary outcome						
Continuous abstinence at end of treatment (wk 9–12) ^e	45 (51)	12 (14)	5 (6)	37 (24–51)	6.5 (3.0–14.1)	<.001
Secondary outcomes						
Continuous abstinence (wk 9–24) ^e	25 (28)	6 (7)	3 (4)	21 (10–33)	6.0 (2.1–16.9)	.001 ^f
Point prevalence abstinence at end of treatment (wk 12) ^e	60 (68)	22 (25)	13 (15)	43 (29–57)	6.1 (3.1–12.2)	<.001 ^f
Abbreviation: aOR, adjusted odds ratio.						
^a Due to outcome missingness, reported counts were computed from the estimated abstinence rates after multiple imputation, rounded to the nearest whole number.						
^b Unadjusted risk differences reported as post hoc descriptive analyses. Values do not equal the simple difference between values in the table due to rounding.						
^c Models fit to data from varenicline and placebo groups only, adjusted for sex and baseline E-cigarette Dependence Inventory score.						
^d Models fit to data from all 3 study groups, adjusted for sex and baseline E-cigarette Dependence Inventory score. Model-based omnibus tests for any difference in abstinence rates across the 3 treatment groups.						
based on χ^2 Wald statistic: week 9–12 abstinence, $\chi^2 = 26.8$ ($P < .001$); week 9–24 abstinence, $\chi^2 = 12.8$ ($P < .001$); week 12 abstinence, $\chi^2 = 28.8$ ($P < .001$). ^e Continuous abstinence defined as observed point prevalence abstinence over specified study visits. Point prevalence abstinence defined as self-report of no e-cigarette use since the last visit, bioverified by saliva cotinine level less than 30 ng/mL (827.64 nmol/L). Visits with self-reported abstinence missing bioverification were treated as missing, with missingness addressed via multiple imputation. ^f Benjamini-Hochberg multiplicity correction applied to P values reported across 5 secondary analysis results (2 indicated varenicline vs placebo comparisons of secondary outcomes and omnibus tests of all 3 outcomes).						

Figure 2. Longitudinal Observations of Nicotine Vaping Abstinence Rates and Nicotine Withdrawal, Craving, and Distress, by Treatment Intervention Group

Panel tables show number of observed outcome measures at each study visit. A, Abstinence rates and Wilson 95% confidence intervals (vertical lines) computed by visit among observed participants. Participants with self-reported

abstinence missing bioverification treated as missing. B-D, Means and Wald 95% confidence intervals (vertical lines) computed by visit among observed participants. See Table 1 footnotes for explanations of scale interpretations.

finding of a benefit of varenicline over behavioral vaping cessation interventions alone in this population. To our knowledge, this is the first pharmacotherapy trial for nicotine vaping cessation in youth.³² Discovering and delivering effective treatments for nicotine addiction, particularly in youth, is important because of converging evidence that earlier age of drug initiation is associated with more rapid transition to substance use disorder and that adolescent nicotine exposure specifically increases subsequent tobacco smoking and other substance use disorders.^{7,33,34} Most youth who develop addiction to vaped nicotine have never regularly smoked tobacco and wish to quit vaping,⁴ highlighting the importance of these findings that an available pharmacotherapy is effective and well tolerated for vaping cessation in this population.

Adverse events with varenicline were similar to those reported in prior trials and included mostly mild to moderate nausea, vivid dreams, and insomnia, with discontinuation of varenicline due to adverse events uncommon.³⁵ Among those assigned to varenicline, 2% discontinued study medication and 5% reduced their dose due to an adverse event. It is reassuring that in this sample, with more than one-half of participants reporting a mental health disorder in addition to tobacco use disorder, consistent with prior reports among youth who vape nicotine,³⁶⁻³⁸ the incidence of neuropsychiatric adverse events did not differ between the varenicline and placebo groups, replicating prior safety and tolerability reports of varenicline in youth.^{39,40} In fact, mood and anxiety adverse events were more common in the placebo group, perhaps

Table 3. Summary of Adverse Events

Outcome	No. (%)		
	Varenicline (n = 88)	Placebo (n = 86) ^a	Enhanced usual care (n = 86)
Any treatment-emergent adverse event	76 (86)	68 (79)	68 (79)
Any NAEI-elicited adverse event ^b	71 (81)	61 (71)	78 (91)
Any serious adverse event ^c	1 (1)	3 (3)	1 (1)
Study medication discontinuation	2 (2)	1 (1)	NA
Reduced study medication dose due to adverse event	4 (5)	1 (1)	NA
Initiated regular combusted tobacco use during the trial ^d	3 (5)	2 (4)	0
Initiated regular combusted tobacco use among those with e-cigarette abstinence at week 24	0	0	0
Postbaseline adverse events	n = 466	n = 358	n = 249
Mild	316 (68)	233 (65)	151 (61)
Moderate	148 (32)	120 (34)	94 (38)
Severe	2 (<1)	5 (1)	4 (2)
Adverse events reported by ≥5% in any group ^e			
Nausea and vomiting symptoms	51 (58)	23 (27)	5 (6)
Cold symptoms	41 (47)	29 (34)	35 (41)
Vivid dreams	34 (39)	14 (16)	0
Insomnia	27 (31)	16 (19)	7 (8)
Bloating	25 (28)	22 (26)	2 (2)
Anxiety disorders and symptoms	22 (25)	28 (33)	30 (35)
Mood disorders and disturbances	22 (25)	27 (31)	21 (24)
Constipation	14 (16)	9 (10)	3 (4)
Headache	11 (13)	18 (21)	6 (7)
Withdrawal symptom	7 (8)	7 (8)	8 (9)
Appetite increased	5 (6)	3 (3)	6 (7)
Chest pain	0	1 (1)	5 (6)

Abbreviations: NA, not applicable; NAEI, Neuropsychiatric Adverse Events Interview.

^a Analysis limited to participants who received randomized treatment. Because 1 participant randomized to placebo did not receive treatment, the denominator for the analysis is 86.

^b Two prespecified pair-wise Fisher exact tests compared proportion of participants with an NAEI-elicited adverse event by week 12: varenicline vs placebo ($P = .16$) and varenicline vs enhanced usual care ($P = .08$).

^c Defined as adverse events resulting in death or that were life-threatening; required hospitalization or prolonged a hospitalization; resulted in persistent or significant disability, incapacity, or congenital abnormality; or that required

medical intervention to prevent any of the above outcomes. The 5 serious adverse events were composed of 1 motor vehicle crash, 1 snowboarding incident, and 3 psychiatric hospitalizations. All psychiatric hospitalizations were reported by participants randomized to placebo or enhanced usual care.

^d No participant who met vaping abstinence criteria initiated regular tobacco smoking, operationalized as smoking more than 5 days per week, during the trial.

^e Includes all treatment-emergent adverse events reported by 5% or more of participants in any study group. Listed in descending order by varenicline group.

reflecting varenicline mitigation of these symptoms that are part of the nicotine withdrawal syndrome. No substitution of combusted tobacco was observed in those who quit vaping nicotine. Progression to regular tobacco smoking was uncommon, reported in 2% of participants by week 24, none of whom had achieved vaping abstinence.

Treatment adherence and study retention were high for a youth sample, which may have contributed to positive findings for nicotine vaping cessation not consistently observed in youth smoking cessation trials.^{39,40} Aspects of the study design, including fully remote, flexibly scheduled behavioral counseling—conducted via Zoom by behavioral counselors who were closely matched in age to participants who followed up participants for the full 12 weeks, enabling development of trust and rapport—and incentivized videorecording of study medication adherence, are novel aspects of the study design that may have enhanced treatment adherence and retention, in-

creasing treatment exposure.⁴¹ It is also possible that framing the intervention as a vaping cessation or reduction intervention rather than a strictly cessation-oriented intervention facilitated enrollment and retention, permitting greater treatment exposure.³²

Limitations

Several limitations should be noted. First, while retention was high in both the varenicline and the placebo groups, intervention uptake was somewhat lower in the placebo group, perhaps reflecting differences in early treatment effects on craving, nicotine withdrawal symptoms, and vaping cessation. While it is possible that lower behavioral counseling attendance in those assigned to placebo could cause lower abstinence rates, the per-protocol analysis excluding participants with less than 80% adherence to study medication and behavioral counseling sessions demonstrated a large difference

between varenicline plus behavioral counseling and placebo plus behavioral counseling among those with high adherence to behavioral counseling. Second, the sample size yielded robust odds ratios for the primary comparison but was underpowered, at 47% power, to detect the observed difference in the exploratory comparison between placebo plus behavioral counseling (14% abstinence) and enhanced usual care (6% abstinence). Third, while the study enrolled youth who did not regularly smoke tobacco, 8% of participants reported some sporadic combustible tobacco use in the 90 days before randomization; however, sensitivity analyses excluding these participants yielded results similar to those from the primary analyses. Fourth, results may not generalize to those who regu-

larly use both combustible tobacco and vaped nicotine, who were excluded and comprised 17% of the screened sample. Additionally, objective measures of TIQ adherence were not available for this study, and TIQ enrollment and interaction was lower than expected in all study groups.⁴²

Conclusions

Varenicline, when added to brief, remotely delivered behavioral counseling, is well-tolerated and promotes vaping cessation compared with placebo in youth with moderate to severe addiction to vaped nicotine.

ARTICLE INFORMATION

Accepted for Publication: March 10, 2025.

Published Online: April 23, 2025.

doi:10.1001/jama.2025.3810

Author Contributions: Drs Evins and Reeder 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.

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Statistical analysis: Reeder, Potter.

Obtained funding: Evins, Schuster.

Administrative, technical, or material support: Evins, Cather, Pachas, Iroegbulem, Dufour, Gilman, Schuster.

Supervision: Evins, Cather, Pachas, Schuster.

Conflict of Interest Disclosures: Dr Evins reported receiving a grant from Charles River Analytics (subcontract for a National Institute on Drug Abuse [NIDA] grant) outside the submitted work. Dr Cather reported receiving a grant from Charles River Analytics (subcontract for a NIDA grant) and receiving consulting fees from Navigate. Dr Pachas reported serving on the Racial Equity Advisory Board and the Scientific Advisory Board for the Massachusetts Department of Public Health Bureau of Substance Abuse Services outside the submitted work. Dr Gray reported receiving consulting fees from Achieve Life Sciences and Indivior and receiving grants from Aelis Farma outside the submitted work. Dr Levy reported previously serving as an expert witness in legal cases against JUUL. Dr Rigotti reported receiving grants from Achieve Life Sciences regarding vaping cessation; receiving personal fees from Achieve Life Sciences ending in 2022; and receiving personal fees from Wolters Kluwer for writing UpToDate reviews of smoking cessation and electronic cigarettes outside the submitted work. Dr Iroegbulem reported grants from NIH outside the submitted work. No other disclosures were reported.

Funding/Support: This study was funded by NIH grants R01DA052583, 3R01DA052583-03S1, and 3R01DA052583-03S2 (Dr Evins and Dr Schuster).

Role of the Funder/Sponsor: The NIH 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.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank the participants in the study. We also thank the data and safety monitoring board (DSMB) members (Nae Yuh Wang, PhD [Johns Hopkins Bloomberg School of Public Health, DSMB chair], Jessica Calihan, MD [Boston Children's Hospital], Jonathan Winickoff, MD, and Colin Burke, MD [Massachusetts General Hospital]) and thank Patricia Mabry, PhD (HealthPartners Institute), for a helpful reading of the manuscript. These individuals did not receive financial compensation for their contributions.

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