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Phase IIb trial of an alpha-7 nicotinic receptor partial agonist with and without nicotine patch for withdrawal-associated cognitive deficits and tobacco abstinence

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Abstract

Purpose/Background—The objective of this study was to determine whether a novel alpha-7 nicotinic acetylcholine receptor (nAChR) partial agonist improves cognition during nicotine withdrawal and improves abstinence rates. To do so, the effect of the alpha-7 nAChR partial agonist, encenicline, on cognition and abstinence was evaluated when given as monotherapy and when combined with transdermal nicotine patch (NRT).

Methods/Procedures—Adult daily smokers, n=160, who were motivated to quit smoking completed cognitive testing at satiated baseline and after overnight abstinence, and then were randomized to receive a 12-week trial of encenicline 1mg twice daily or identical placebo the day of the overnight abstinent cognitive testing. In the first 6 weeks of the 12-week encenicline administration, participants were also randomized to 6 weeks of NRT patch or placebo patch. Primary outcomes were cognition during abstinence and seven-day point-prevalence abstinence at week 12.

Findings/Results—No beneficial effects of encenicline were observed on cognition or abstinence when compared to placebo or when combined with NRT compared to placebo capsule + NRT. Of the 4 conditions, abstinence rates were lowest amongst those assigned to encenicline alone.

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Implications/Conclusions—Beneficial effects of NRT were observed on cognitive and abstinence outcomes when combined with encenicline compared with encelicline plus placebo patch. Addition of NRT to encenicline improved odds of abstinence approximately 3-fold compared to encenicline plus placebo patch. We conclude that encenicline, 1mg per day, did not improve abstinence-associated cognitive impairment or abstinence rates as monotherapy or adjunctive therapy to NRT patch.

Keywords

Smoking Cessation; Encenicline [EVP-6124]; EVP-6124; Nicotine; Cognition; Withdrawal

Introduction

Cigarette smoking remains the leading preventable cause of death in the developed world. Smoking is estimated to cause over 440,000 deaths in the United States annually and over \$193 billion in annual health-related economic losses¹. Approximately half of the world's current daily cigarette smokers who do not quit will die prematurely of causes that could be prevented by treatment of their addiction to tobacco-delivered nicotine^{2,3}. While pharmacotherapy is universally recommended for smoking cessation⁴, and first line cessation aids double to triple sustained abstinence rates over placebo⁵⁻¹¹, studies have consistently found that 60-70% of smokers fail to attain abstinence with currently available therapies on any given attempt¹²⁻¹⁶. Reducing smoking prevalence by increasing cessation among current smokers is critical in reducing tobacco-related mortality in the near future.

Cognitive deficits are commonly experienced during nicotine withdrawal and may increase the likelihood of failure to attain abstinence and early relapse. "Difficulty concentrating," as noted in the Diagnostic and Statistical Manual–Fifth Edition (APA, 2013), is commonly endorsed in prospective studies of withdrawal^{17,18}. Behavioral impairments with withdrawal have been most commonly found in the domains of sustained attention and working memory¹⁹⁻²¹, and are reversed by nicotine re-exposure thus supporting the causal role of nicotine abstinence on emergent deficits²²⁻²⁶. Rodent models using the 5-choice serial reaction time task^{27,28} and human models using measures of sustained visual attention^{24,29-34} find increased omissions, decreased response accuracy and increased variability in response speed within the first few hours of nicotine abstinence. Abstinence-induced impairments are also found on visual working memory tasks^{24,35-38}, particularly as cognitive load increases³⁹. These deficits are hypothesized to be modulated by decreased activation in executive control regions (e.g., dorsolateral prefrontal cortex)^{35,40-43} and an overall weaker inhibition of the default mode network during abstinence^{44,45}, as well as activity at the alpha-7 nicotinic acetylcholine receptor (nAChR)⁴⁶.

Further, cognitive deficits emergent during nicotine withdrawal predict relapse to smoking⁴⁷⁻⁵¹, likely due to a combination of processes including negative reinforcement (i.e., resumption of nicotine quickly alleviates cognitive deficits), drug-reward bias (i.e., increased salience of drug stimuli), as well as goal and skill interference (i.e., cognitive skills impaired by abstinence underlie effective use of coping skills)⁵². For example, working memory deficits following three days of abstinence predict cessation outcomes among

untreated smokers^{49,50}. One of the mechanisms of action of smoking cessations aids such as varenicline may be amelioration of withdrawal-associated cognitive impairment^{53,54}, supporting the hypothesis that cognitive enhancing agents may improve smoking cessation rates.

This project aims to discover whether a novel compound, targeting cognitive symptoms that worsen during early withdrawal from nicotine and are associated with early relapse, can ameliorate these symptoms and whether this, in turn, improves smoking cessation outcomes. To do so, we conducted a Phase IIb trial of the effects of the selective alpha-7 nAChR agonist, encenicline (EVP-6124; (R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide), as monotherapy and when combined with transdermal nicotine patch (NRT), on cognitive performance during early nicotine abstinence and on abstinence rates. Alpha-7 nAChRs are one of two principal nAChRs in the brain. They are ligand-gated cation channels, highly expressed in regions involved in cognitive function including hippocampus, cortex, and subcortical limbic regions⁵⁵. Alpha-7 nAChRs are associated with cholinergic, dopaminergic and glutamatergic transmission^{56,57}, and are thought to mediate the pro-cognitive effects of nicotine. Alpha-7 nAChRs are less sensitive to nicotine's effects than the more common neuronal alpha-4 beta-2 nAChRs^{58,59}. Typical doses of NRT, e.g. a 21-mg patch, only replace 60% of the nicotine taken in by a one pack per day smoker, and the kinetics of NRT produce lower peak nicotine concentrations than smoked tobacco. Thus, it is likely that recently abstinent smokers using NRT experience reduced alpha-7 nicotinic receptor stimulation than while smoking. Selective alpha-7 nAChR agonists⁶⁰ have shown pro-cognitive effects in animals⁶¹⁻⁶⁴, healthy volunteers^{65,66}, and adults with schizophrenia⁶⁶⁻⁶⁹. Addition of an alpha-7 nAChR agonist could restore alpha-7 activity during early abstinence and may improve cognitive and abstinence outcomes when combined with NRT, which would primarily bind the high affinity alpha-4 beta-2 receptors and blunt withdrawal symptoms and craving.

Encenicline is a potent alpha-7 nAChR agonist that has good oral bioavailability and enters the brain readily (see⁷⁰ for compound structure). Encenicline is an antagonist of the serotonin₃ (5-HT₃), serotonin_{2A} (5-HT_{2A}), and 5-HT_{2B} receptors, and has very limited or no activity on other receptors⁷⁰. At higher concentrations, it is a positive modulator of the alpha-4 beta-2 subtype nAChR. In a study of healthy adults, encenicline was found to be well tolerated, detectable in plasma at single doses between 1 mg and 180 mg, have linear kinetic effects with maximum plasma concentration occurring between 5 and 8 hours, and have a half-life of 54 to 62 hours⁶⁶. The pharmacokinetic profile of the drug was found to be impacted by body weight but not food⁶⁶. Studies in animals suggest that the major metabolic pathways for encenicline involve oxidation, glucuronide, and sulfate conjugations, while the minor pathway involves dechlorination and O-methylation. Human studies indicate low hepatic clearance compared to animals. Chances of drug interactions via cytochrome P450 enzymes are suspected to be low; however, other mechanisms of degradation are not yet known (EVP-6124 Investigator's Brochure, Version 5.0).

Several studies support the pro-cognitive effects of encenicline. Nonclinical trials support the efficacy of encenicline at improving visual recognition memory⁷⁰ and attention, vigilance and impulsivity⁶². Phase 1 studies with encenicline in healthy young volunteers⁶⁶

as well as Phase 1 and 2 studies in subjects with Schizophrenia taking atypical anti-psychotics^{67,68} and subjects with Alzheimer's disease with or without concomitant acetylcholinesterase inhibitor medication⁷¹ have provided evidence of cognitive enhancement as assessed with the CogState battery. It is postulated that the effects of encenicline on improved cognition may be mediated by modulation of multiple neurotransmitter systems including dopamine, acetylcholine, and glutamate in the prefrontal cortex and other brain regions⁷².

The primary aims of this trial were to establish whether encenicline monotherapy or combination therapy with NRT 1) can ameliorate withdrawal-associated cognitive impairment, and 2) is associated with improved 12-week smoking cessation outcomes. We hypothesized that subjects randomized to encenicline + NRT patch or encenicline + placebo patch would demonstrate superior performance on a cognitive battery and have lower relapse rates than those assigned to placebo capsule + NRT or placebo capsule + placebo patch.

Materials and Methods

All participants gave written informed consent to the Partners' Human Subjects Review Committee approved protocol prior to initiating study procedures. Study procedures were conducted between January 2012 and September 2015 at the Center for Addiction Medicine and the Depression Clinical and Research Program at the Massachusetts General Hospital in Boston, Massachusetts. Study procedures were terminated prematurely due to an FDA clinical hold all clinical trials of encenicline due to reports of serious gastrointestinal adverse events in study participants with dementia of the Alzheimer's type. The trial was concluded with 41% of planned enrollment.

Study Population

Eligible participants were otherwise healthy, aged 18 to 65 years, who smoked 10 cigarettes/day during the prior six months, had expired carbon monoxide of 10 parts per million (ppm) at screening, reported smoking within 30 minutes of awakening, were fluent in English, and willing to set a quit date within four weeks of enrollment. Those who had an alcohol or other drug use disorder within the past six months, had a lifetime psychotic, bipolar, pervasive developmental disorder or current major depressive disorder, or who were pregnant or lactating were excluded. See Supplemental Digital Content 1 for full inclusion/exclusion criteria. Participants were recruited using local media advertisement and physician referral.

Study Design

This was a Phase IIb, randomized, double-blind, placebo-controlled, parallel-group, two by two design treatment trial designed to evaluate of effects of encenicline monotherapy and combination therapy with NRT patch on cognitive and abstinence outcomes in smokers with nicotine use disorder. Eligible participants participated in two baseline cognitive assessments: a satiated (non-abstinent) baseline and a 24-hour abstinent baseline. Participants were considered to have achieved 24-hour abstinence if they reported not smoking for 18 to 24 hours and had an expired CO <10 ppm in those smoking less than or

equal to one pack per day and CO of <15 ppm in those smoking more than one pack per day. Participants who did not arrive in an abstinent state by these criteria were provided another opportunity within 10 days to complete the abstinent baseline assessment. Participants who had two failures to achieve abstinence for the abstinent baseline assessment were not eligible for randomization and were referred for clinical smoking cessation treatment.

Eligible participants who completed both satiated and abstinent baseline assessments were randomized to one of four treatment groups, using a stratified 16-block randomization procedure. Stratification variables were sex and severity of nicotine dependence based on the Fagerstrom Test for Cigarette Dependence (FTCD)⁷³ total score obtained at screening (score of six or higher (severe dependence), or score of less than six (low to moderate dependence). Treatments included: (1) encenicline 1 mg capsule plus NRT transdermal patch (encenicline + NRT); (2) encenicline 1 mg capsule plus placebo patch (encenicline + PP); (3) placebo encenicline capsule plus NRT transdermal patch (PC + NRT); and, (4) placebo encenicline capsule plus placebo patch (PC + PP). Immediately following completion of the abstinent baseline assessment, randomization status was assigned, study medication was distributed, and the first dose of study drug was observed being taken in the clinic and the patch was placed with instructions for future placement and use.

Assessments during the treatment phase were conducted at weeks 1, 2, 4, 6, 8, 10 and 12. At week 12 or early termination, all participants were asked to complete a final assessment including those who prematurely discontinued study treatments. This study also included a one- and two-week follow-up safety assessment (data not presented).

Study Interventions

During the 12-week treatment period, participants ingested an oral dose (one capsule) of study drug (encenicline 1 mg or identical appearing PC) in the morning and applied one transdermal patch (NicoDerm CQ or identical appearing PP) daily on days one to 42, on a taper schedule involving the use of 21 mg per day for weeks 1 through 3, 14 mg per day for weeks 4 and 5, and 7 mg per day for week 6 (last dose on day 42 ± 3 days). Adherence to study drug was assessed by recording the number of capsules and patches dispensed and returned at every study visit. Participants were offered brief (<10 minutes) cognitive behavioral therapy (CBT) sessions at each of nine study visits during double-blind treatment based on the Freedom from Smoking curriculum from the American Lung Association (<http://www.ffsonline.org/>).

Outcome Measures

The primary cognitive endpoints were performance on the Conners Continuous Performance Task (CPT), a measure of attentional control and response inhibition⁷⁴, and the N-Back task, a standard measure of working memory under varying levels of task demand. These measures are sensitive to the effects of nicotine^{19,75-80}, abstinence^{49,81,82}, and other nAChR agonists⁵³. During the CPT, participants were asked to press a button as quickly as possible whenever a letter appeared on a computer screen unless that letter was an 'X'. Hit RT and hit RT standard error were primary outcomes of interest. On the N-back task, participants were asked to indicate if a stimulus presented one at a time sequentially, was identical to the

stimulus presented N items prior, where N equals one, two or three⁸³. N-back outcomes of interest were reaction time (RT) on two- and three-back levels. Cognitive tests were performed at the satiated and abstinent baseline visits and the study week 1, 2, 6, and 12 visits.

The primary smoking-related endpoint was self-report of seven-day point prevalence tobacco abstinence using the Timeline Follow-back method⁸⁴, biochemically verified by expired air CO levels <10 and urine cotinine <50 ng/ml⁸⁵.

Safety Assessments

Safety assessments included physical examinations, routine laboratory assessment, 12-lead electrocardiogram (EKG), concomitant medications, urinalysis and screen for illicit drugs, and treatment-emergent adverse events (AEs). Safety assessments also comprised nicotine craving and withdrawal assessments, including the Wisconsin Smoking Withdrawal Scale (WSWS;⁸⁶) and the Tiffany Questionnaire of Smoking Urges (TQSU)⁸⁷, as well as psychiatric measures such as the Positive and Negative Affect Scale (PANAS-X)⁸⁸, Center for Epidemiologic Studies – Depression (CES-D)⁸⁹, and Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)⁹⁰. To monitor safety during treatment, EKG was conducted at baseline and weeks 1, 2, 6, and 12; lab tests were conducted at weeks 1, 4, 6, and 12. If clinically significant laboratory test abnormalities emerged during treatment, participants were notified and either discontinued if deemed appropriate or advised to seek care as appropriate through their regular physician.

Statistical Analysis

Analyses were conducted with the modified intent-to-treat population that included participants who received at least one dose of study medication and returned for at least one post-baseline assessment (n=160). To examine changes in cognitive performance from satiated to abstinent baseline assessments, paired t-tests were conducted separately for each cognitive measure among those who achieved overnight abstinence.

The cognitive models to study the average effect of treatment on cognitive performance over 12 weeks after adjusting for baseline included only data from visits at which the participant had verified seven-day point prevalence abstinence. Marginal structural models were conducted to correct for the fact that abstinent patients were not a random subgroup of the sample^{91,92}. Significant average effects were followed-up at each study visit using the same model. In the marginal structural models, parameters were estimated using a derived weight, which was the inverse probability of being abstinent, multiplied by the group-specific abstinence rate. The predicted probability at week 1 was estimated using logistic regression on identified predictors from forward selection with 0.1 as entry p-value. Candidate predictors had known association with abstinence, and included age, gender, education level, expired CO, total CES-D score, IQ, lifetime problem alcohol use, age of smoking initiation, FTCD total score, total WSWS score, total TQSU score, desire to quit smoking, length of longest prior abstinence, and negative and positive affect scores (PANAS-X). Forward model selection identified total TQSU, expired CO, negative affect score and longest duration of abstinence as significant predictors of abstinence (AUC=0.72). After week 1, logistic

regression with repeated measures was conducted to assess the predicted probability of abstinence, which included total TQSU, expired CO, negative affect, and longest duration of abstinence as covariates, as well as the effect of time and prior abstinence status. Effects were estimated using generalized estimating equations with an autoregressive variance-covariance matrix. Final models predicting probability of being abstinent at week 1 and after week 1 are presented in Supplemental Digital Content 2.

Abstinence models included all participants, and assumed non-abstinence when there were missing abstinence data at any visit. Logistic regression with repeated measures was used to study the average drug effect on probability of abstinence. Effects were estimated using generalized estimating equations with an unstructured variance-covariance matrix. Significant average effects were followed-up at each study visit using the same model. Data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC). An alpha of $p < 0.05$ (two-tailed) was considered statistically significant.

Results

Study Sample

Of 346 smokers who consented to participate in the study, 240 were eligible, 181 completed the satiated and overnight abstinent baseline cognitive assessments, were randomized, and received study medications, and 160 (88.4% of those randomized) completed at least one post-randomization study visit and were included in the analysis (See Consort Diagram, Supplemental Digital Content 3). The groups were well-matched on demographic, educational, smoking, psychiatric and substance use characteristics (Table 1). There was no group difference in study visit attendance (encenicline + NRT: M: 7.7, range: 3 - 9; encenicline + PP: M: 6.5, range: 3 - 9; PC + NRT: M: 7.4, range: 3 - 9; and PC + PP: M: 7.0, range: 2 - 9).

Cognitive Effects

Supplemental Digital Content 4 depicts raw cognitive scores by visit and treatment group.

Cognitive Effects with Overnight Abstinence—Hit RT and hit RT SE increased from satiated (Hit RT: M = 424.08ms, SD = 71.57ms; Hit RT SE: M = 5.37ms, SD = 4.03ms) to abstinent baseline (Hit RT: M = 431.21ms, SD = 70.75ms; Hit RT SE: M = 6.32ms, SD = 3.18ms) on the CPT (p -values < 0.047). RT also increased on the 2-back (Satiated baseline: M = 586.98ms, SD = 162.15ms; Abstinent baseline: M = 632.95ms, SD = 177.15ms; $p = 0.0002$) but not 3-back level of the N-back (Satiated baseline: M = 622.10ms, SD = 182.45ms; Abstinent baseline: M = 633.63ms, SD = 193.64ms; $p = 0.38$).

Cognitive Effects of Encenicline (Supplemental Digital Content 5)—There was no beneficial cognitive effect for encenicline monotherapy compared to placebo when averaged across the 12-week trial. No significant effects of encenicline monotherapy were detected for CPT performance, and those on encenicline + PP had longer reaction times than those on PC + PP on the 2-back level of the N-back (Table 2).

There was also no cognitive benefit observed of encenicline when added to NRT compared to PC + NRT when averaged across the 12-week trial. On the CPT RT, those assigned to encenicline + NRT performed slower on average than those on PC + NRT, and there were no significant treatment effects on N-back performance (Table 2).

Cognitive Effects of NRT (Supplemental Digital Content 5)—A beneficial effect of NRT added to encenicline was observed over encenicline + PP. Those on encenicline + NRT performed faster than those on encenicline + PP on the 2-back level of the N-back, and this effect was greater than the effect of NRT alone (i.e., PC + NRT vs. PC + PP). On average, those randomized to PC + NRT were not different from those on PC + PP on any cognitive measure when averaged across the 12-week trial (Table 3).

Abstinence Outcomes

At week 4 prior to the NRT taper, seven-day point prevalence abstinence rates were highest for those on NRT alone (44.7%), followed by NRT with encenicline (40.0%), PC + PP (19.5%), and encenicline alone (17.1%).

When averaged across the 12-week trial, abstinence rates were not higher with encenicline than with placebo when used as monotherapy (encenicline + PP vs PC + PP; $\chi^2 = 0.54$, $p=0.46$; 95% CI: 0.26, 1.84), or when combined with NRT (encenicline + NRT vs PC + NRT; $\chi^2 = 0.60$, $p=0.44$; 95% CI: 0.63, 2.95; Figure 1 for abstinence rates by week). However, adding NRT to encenicline significantly improved odds of abstinence relative to encenicline alone; those on encenicline + NRT had a 3.24 times greater odds of being abstinent compared to those on encenicline + PP ($\chi^2 = 6.85$, $p=0.009$; 95% CI: 1.34, 7.82), an effect that was significant at weeks 2 (OR = 4.04; $\chi^2 = 7.31$, $p=0.007$; 95% CI: 1.47, 11.09), 4 (OR = 3.59; $\chi^2 = 5.58$, $p=0.02$; 95% CI: 1.24, 10.35), 6 (OR = 4.86; $\chi^2 = 9.78$, $p=0.002$; 95% CI: 0.59, 2.57), and 10 (OR = 3.28; $\chi^2 = 4.96$, $p=0.03$; 95% CI: 1.15, 9.32; p -values for this comparison at weeks 8 and 12 > 0.06 ; Figure 1).

Though seven-day point prevalence abstinence rates were higher at week 4 prior to the NRT taper in the NRT only control than placebo (PC + PP; $p=0.01$), abstinence rates were not higher for PC + NRT vs. PC + PP for the entire study period that included two week NRT taper and six weeks with no NRT ($\chi^2 = 1.28$, $p=0.26$; 95% CI: 0.69, 4.00).

Safety

There were 13 adverse event categories in which 5% of participants reported an occurrence at any time point during the 12-week treatment phase. See Table 2. Constipation was the most common AE. Headache, stomachache, and muscle spasm were more common in the EVP arms than in the placebo pill arms of the trial. There were no serious adverse events.

Discussion

The selective α -7 nAChR partial agonist, encenicline, at a dose of 1mg per day, was not effective for improving attention or memory performance during early abstinence, nor for improving abstinence rates when given as monotherapy or in combination with NRT. NRT

patch, during active dosing prior to dose taper, had modest positive benefits on cognition and on abstinence when given as monotherapy and in combination with encenicline, providing a positive control for the negative findings for encenicline^{75,93-95}. It is expected that NRT did not have a positive effect on cognition over the entire time course of the trial because NRT was only dosed for six weeks with a two-week taper and discontinued for the final six weeks of the trial.

Results are unexpected, given previous reports of pro-cognitive effects of encenicline. Pro-cognitive effects of encenicline have been reported in pre-clinical work in which single⁷⁰ and chronic doses⁹⁶ improved memory performance on delay-dependent forgetting tasks. In clinical trials, adjuvant encenicline showed significant pro-cognitive effects on cognitive and functional measures in medical⁷¹ and psychiatric⁶⁸ populations. Alpha-7 nAChR agonists, GTS-21, SSR180711, and S 24795, improve learning and memory performance in animals (for review, see⁹⁷⁻⁹⁹) and humans^{65,100}. Varenicline, a partial $\alpha 4\beta 2$ agonist and full $\alpha 7$ nAChR agonist, also improves nicotine withdrawal-associated deficits in learning and memory^{53,101}.

Although encenicline has been shown to have pro-cognitive effects at low single-dose nanomolar concentrations⁷⁰, it is possible that the 1mg dose administered in this study was insufficient when chronically administered and that higher doses may be required to obtain pro-cognitive effects in this population. Barbier and colleagues⁶⁶ demonstrated that encenicline was well tolerated up to doses of 180mg and speculated that 2 to 4mg per day may be needed to optimize pro-cognitive effects. Effects of receptor desensitization or tolerance are an unlikely explanation for the negative findings, as cognitive improvement was not evident with encenicline monotherapy or combined with NRT even in study weeks 1 and 2, and prior studies do not support tolerance effects with chronic dosing of nAChR agonists, including encenicline^{96,102,103}. Further, the cognitive tasks were chosen to minimize practice effects and were given to all groups at the same time intervals; therefore, any practice effect should be comparable across groups and not influence findings. Given that we did not observe a significant placebo or practice effect on cognitive task performance, these factors are unlikely to explain the negative finding for encenicline on withdrawal-associated attention and memory. Additionally, we observed significant worsening of cognition after overnight abstinence, with small effect sizes (Cohen's *d* ranging from 0.16 to 0.30), comparable to the degree of worsening observed in other studies^{21,104,105}. Thus, it is unlikely that insufficient test sensitivity and/or a ceiling effect explained the lack of effect of encenicline on cognition.

Study findings also do not support encenicline, at a dose of 1mg per day, as an effective smoking cessation aid. Subjects randomized to encenicline alone did not have better odds of achieving abstinence over 12 weeks than those on placebo. Conversely, abstinence rates were numerically but not significantly lower with encenicline alone than with placebo. Further, when added to NRT, encenicline did not enhance the effect of NRT. However, NRT increased the odds of abstinence 3-fold when combined with encenicline compared to encenicline alone, replicating a large body of research supporting the efficacy of NRT when combined with other treatments^{15,106,107} and improving confidence in the null findings of encenicline as a therapeutic agent for smoking cessation. While the odds of abstinence were

not higher for NRT relative to placebo for the entire period that included NRT taper and no NRT, abstinence rates were more than doubled with active rather than placebo NRT, and abstinence rates were higher in subjects assigned to NRT versus placebo at week 4 prior to the NRT taper. It is also noteworthy that the placebo response, averaging 21.6% abstinence, was rather high compared to other trials assessing abstinence over the time frame^{15,106,107}, which may have minimized our ability to detect abstinence differences with both NRT conditions. This high placebo response may potentially be due to the requirement for overnight abstinence prior to randomization and inclusion of an effective smoking cessation CBT intervention for all participants.

Findings should be interpreted in the context of the following limitations. Due to an FDA clinical hold on clinical trials of encenicline, enrollment was halted prior to the target enrollment of 96 participants per arm, resulting in reduced power to detect treatment effects on cognition and abstinence or moderators of treatment effects, such as sex, which has been shown to influence the pharmacokinetic profile of encenicline⁶⁶. The rapid NRT taper may underlie the rapid relapse rate observed in the NRT arms, but is unlikely to have impacted our ability to detect an effect of encenicline, as there was no evidence that encenicline enhanced cognition or abstinence prior to the NRT taper.

To our knowledge, this was the first study to evaluate a putative alpha-7 agonist cognitive enhancing agent for smoking cessation. Although encenicline, at the dose tested, did not improve cognitive performance during early nicotine withdrawal, further efforts are warranted to test the hypothesis that a cognitive enhancing agent can ameliorate withdrawal-associated cognitive impairment and, through this mechanism, may improve abstinence rates either alone or in combination with a first line pharmacotherapeutic smoking cessation aid.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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* Week 2 p-value = 0.02

Encenicline + NRT > Encenicline + Placebo Patch

^x Week 4 p-value = 0.01

Encenicline + NRT > Encenicline + Placebo Patch

Placebo Capsule + NRT > Placebo Capsule + Placebo Patch

[^] Week 6 p-value = 0.002

Encenicline + NRT > Encenicline + Placebo Patch

⁺ Week 10 p-value = 0.07

Encenicline + NRT > Encenicline + Placebo Patch

All other comparisons were non-significant. P-values are from omnibus models. Pairwise comparisons are Fisher's exact tests.

Figure 1. Seven-Day Point Prevalence Abstinence by Group across 12 Weeks of Treatment

Figure 1 shows differences in seven-day point prevalence abstinence, by group, across the 12-week trial. NRT was associated with improved abstinence rates at week 2, 4, 6 and 10 compared to encenicline + placebo patch, and week 2 only compared to placebo capsule + placebo patch.

Table 1

Baseline Participant Characteristics

	Enrolled, Not Analyzed (n=80)	Encenicline (n=81)		Placebo Capsule (n=79)	
		NRT patch (n=40)	Placebo Patch (n=41)	NRT patch (n=38)	Placebo patch (n=41)
Demographics					
Age	44.63 (11.00)	42.63 (12.17)	44.70 (13.06)	44.03 (12.81)	45.15 (11.42)
Gender (% Male)	63.8%	65.0%	65.9%	65.8%	58.5%
Race/Ethnicity					
White	68.7%	75.7%	87.2%	76.3%	73.2%
Black	23.8%	18.9%	7.7%	18.4%	24.4%
Other	7.5%	5.4%	5.1%	5.3%	2.4%
Ethnicity (% Hispanic)	13.8%	20.0%	9.8%	7.9%	2.4%
Marital Status (% Married)	32.5%	32.5%	34.1%	39.5%	34.1%
Education History					
% Finished High School	93.8%	100.0%	92.7%	97.3%	95.1%
% Finished College	30.0%	30.0%	24.4%	29.7%	31.7%
IQ	97.01 (13.48)	103.80 (12.10)	99.27 (15.09)	100.97 (13.85)	99.39 (17.17)
Smoking Characteristics					
Years of Regular Smoking	25.15 (10.91)	23.31 (11.01)	26.38 (13.24)	24.89 (12.84)	26.46 (12.17)
Cigarettes Smoked Per Day	22.19 (17.84)	18.53 (9.35)	19.41 (15.09)	22.87 (30.63)	20.04 (13.85)
Expired CO, ppm	19.01 (10.41)	18.83 (11.97)	16.39 (9.40)	17.87 (9.87)	16.95 (9.19)
FTCD Score	5.90 (1.89)	5.40 (2.07)	5.34 (2.17)	5.39 (1.94)	5.32 (2.07)
Longest Cessation Attempt (wks)	24.73 (65.88)	74.21 (235.36)	56.48 (117.36)	41.24 (94.45)	65.16 (116.67)
QSU Score	39.39 (14.68)	44.63 (14.89)	37.80 (14.09)	39.18 (14.57)	40.61 (15.31)
WSWS Score	48.29 (13.59)	51.78 (16.83)	49.38 (14.09)	49.68 (16.50)	52.24 (11.98)
Lifetime SUDs (SCID-IV)					
Alcohol	37.1%	35.5%	17.1%	45.2%	40.0%
Cannabis	15.9%	15.6%	17.1%	9.4%	11.8%

	Enrolled, Not Analyzed (n=80)	Encenicline (n=81)		Placebo Capsule (n=79)	
		NRT patch (n=40)	Placebo Patch (n=41)	NRT patch (n=38)	Placebo patch (n=41)
Other	25.7%	12.6%	11.4%	28.1%	11.8%
<i>Psychiatric Characteristics</i>					
CES-D Total	7.74 (5.63)	10.00 (10.91)	10.41 (7.38)	9.29 (6.86)	8.44 (5.40)
ASRS Total*	1.14 (1.55)	2.30 (1.68)	1.95 (1.58)	1.92 (1.85)	1.88 (1.62)
Lifetime Depression (SCID-IV)	8.6%	12.5%	2.9%	12.5%	17.1%
Any Lifetime Anxiety Dx (SCID-IV)	9.0%	9.4%	2.9%	3.2%	0%

* Enrolled, Not Analyzed < Encenicline + NRT Patch, Encenicline + Placebo Patch, Placebo Capsule + NRT Patch, Placebo Capsule + Placebo Patch; p-values < 0.02.

Note. All values are means and standard deviations at screening unless otherwise noted. Unless indicated, there were no significant between-group differences in baseline characteristics in groups. Abbreviations: ASRS, Adult ADHD Self-Report Scale, for which scores 24 or higher in a range of 0 to 72 indicate a high likelihood of having ADHD; CES-D, Center for Epidemiologic Studies-Depression Scale, with higher scores (range: 0 to 60) suggestive of depression; CO, carbon monoxide; Dx, disorder; FTCD, Fagerstrom Test for Cigarette Dependence, for which scores of 6 or higher in a range of 0 to 10 indicate severe dependence; SCID-IV, Structured Clinical Interview for DSM-IV.

Table 2

Average Effects of Encenicline on Cognition with and without NRT.

Cognitive Task	Effect of Encenicline Averaged Across 12-Week Trial							
	Without NRT (Comparison: Encenicline + Placebo Patch vs Placebo Capsule + Placebo Patch)				With NRT (Comparison: Encenicline + NRT vs Placebo Capsule + NRT)			
	Estimate	95% CI	Chi-Square	P-Value	Estimate	95% CI	Chi-Square	P-Value
CPT Hit RT (ms)	1.25	-34.56, 37.07	0.005	0.95	19.55	1.53, 37.57	4.52	0.03**
CPT Hit SE (ms)	0.34	-1.72, 2.41	0.11	0.74	0.82	-0.43, 2.07	1.65	0.20
N-Back 2-Back RT (ms)	71.99	0.45, 143.52	3.89	0.049*	-21.40	-77.88, 35.08	0.55	0.46
N-Back 3-Back RT (ms)	111.20	-28.49, 250.89	2.43	0.12	-32.83	-173.24, 107.58	0.21	0.65

* Evaluating this effect by week, those on encenicline + placebo patch performed faster than those on placebo capsule + placebo patch at week 2 ($\chi^2 = 7.26$, $p=0.007$; 95% CI: -199.89, -31.55), and slower at week 6 ($\chi^2 = 14.99$, $p = 0.0001$; 95% CI: 100.89, 307.74; p -values at other time points > 0.09).

** Evaluating this effect by week, those on encenicline + NRT performed slower at weeks 6 ($\chi^2 = 4.99$, $p=0.03$; 95% CI: 2.29, 35.18) and 12 ($\chi^2 = 12.78$, $p=0.0003$; 95% CI: 18.43, 63.14; p -values at other time points > 0.25) than those on placebo capsule + NRT.

Note. All effects are estimated from weighted abstinent patients.

Abbreviations: CI, Confidence interval; CPT, Conners Continuous Performance Test; NRT, Nicotine replacement therapy; RT, Reaction time; SE, Standard error

Table 3

Average Effects of NRT on Cognition with and without Encenicline.

Cognitive Task	Effect of NRT Averaged Across 12-Week Trial							
	Without Encenicline (Comparison: Placebo Capsule + NRT vs Placebo Capsule + Placebo Patch)				With Encenicline (Comparison: Encenicline + NRT vs Encenicline + Placebo Patch)			
	Estimate	95% CI	Chi-Square	P-Value	Estimate	95% CI	Chi-Square	P-Value
CPT Hit RT (ms)	2.37	-21.23, 25.97	0.04	0.84	20.67	-7.14, 48.48	2.12	0.15
CPT Hit SE (ms)	-0.42	-1.57, 0.73	0.51	0.48	0.05	-2.10, 2.20	0.002	0.96
N-Back 2-Back RT (ms)	2.39	-53.41, 58.19	0.01	0.93	-90.99	-164.32, -17.67	5.92	0.02 *
N-Back 3-Back RT (ms)	160.94	-19.20, 341.08	3.07	0.08	16.91	-78.35, 112.17	0.12	0.73

* Evaluating this effect by week, those on encenicline + NRT performed faster than those on encenicline + placebo patch at week 6 ($\chi^2 = 14.34$, $p=0.0002$; 95% CI: -196.29, -62.39; p-values at other time points > 0.10).

Note. All effects are estimated from weighted abstinent patients.

Abbreviations: CI, Confidence interval; CPT, Conners Continuous Performance Test; NRT, Nicotine replacement therapy; RT, Reaction time; SE, Standard error

Table 4

Adverse Events

Adverse Event ^a (week 1-12)	Number (%) of Participants ^b			
	EVP-6124 (n=81)		Placebo Capsule (n=79)	
	NRT (Group 1; n=40)	Placebo NRT (Group 2; n=41)	NRT (Group 3; n=38)	Placebo NRT (Group 4; n=41)
Constipation	11 (27.5)	8 (19.5)	8 (21.1)	5 (12.2)
URI	10 (25.0)	4 (9.8)	7 (18.4)	7 (17.1)
Elevated CPK	2 (5.0)	0 (0)	4 (10.5)	3 (7.3)
Headache ^c	10 (25.0)	2 (4.9)	2 (5.3)	4 (9.8)
Cold/Flu	7 (17.5)	3 (7.3)	7 (18.4)	3 (7.3)
Skin Irritation at Patch Site ^d	12 (30.0)	3 (7.3)	2 (5.3)	3 (7.3)
Fatigue	5 (12.5)	2 (4.9)	2 (5.3)	2 (4.9)
Insomnia	6 (15.0)	3 (7.3)	6 (15.8)	5 (12.2)
Stomachache ^e	3 (7.5)	5 (12.2)	0 (0)	0 (0)
Irritability	4 (10.0)	1 (2.4)	1 (2.6)	3 (7.3)
Muscle Spasm ^f	7 (17.5)	2 (4.9)	0 (0)	1 (2.4)
Allergies	6 (15.0)	2 (4.9)	3 (7.9)	3 (7.3)
Abnormal Dreams	5 (12.5)	1(2.4)	5 (13.2)	2 (4.9)

^aAdverse events that occurred in at least 5% of the participants at any point between Weeks 1 and 12 of the trial.

^bNumbers are presented as the total number of participants per treatment group who endorsed an adverse event at least once in a 12-week period.

^cP<0.05 Fisher exact test (1 > 2, 3).

^dP<0.05 Fisher exact test (1 > 2, 3, 4).

^eP<0.05 Fisher exact test (2 > 3, 4).

^fP<0.05 Fisher exact test (1 > 3; 1 > 4).

Abbreviations: URI – upper respiratory infection, CPK – creatine phosphokinase blood test.