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The Safety and Efficacy of Varenicline in Cocaine Using Smokers Maintained on Methadone: A Pilot Study

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Abstract

In this double-blind, placebo-controlled trial, we compared varenicline (2 mg) to placebo for treatment for cocaine and tobacco dependence in 31 methadone-maintained subjects. Subjects received weekly counseling during the 12-week study participation. Our results indicate that varenicline is safe to give to this subject population, as there were no adverse events related to medication during this study. Varenicline was no more effective than placebo for abstinence from cocaine. Treatment with varenicline was associated with a reduced number of cigarettes smoked per day, even though subjects received only a brief education for smoking cessation. The self-report reduction in smoking was corroborated by CO levels and the Fagerström Test of Nicotine Dependence. However, self-ratings of positive mood on the Positive Affect Negative Affect Schedule did significantly decrease in the varenicline group as compared to the placebo group, although this appears to be due to randomization differences related to lifetime depression diagnosis. These preliminary findings may point to potential therapeutic value of varenicline for smoking cessation in cocaine users maintained on methadone.

INTRODUCTION

Cocaine addiction continues to be an important public health problem in the United States (U.S.) with a significant cost to the individual and society. Among substance abusers, cocaine use has been recognized as a significant problem especially in methadone-maintenance patients. In several studies, rates of cocaine use have been reported to range from 30 to over 60% of those in methadone maintenance programs.[1–3] In these patients, cocaine use seems to be a predictor of poor clinical outcome.[4,5] Consequently, the development of effective pharmacotherapies for cocaine use disorders, especially in the opioid-dependent population, is of great importance. Unfortunately such effective pharmacotherapies do not currently exist.[6]

An epidemiological connection between cocaine use and cigarette smoking has long been noted.[7] Cocaine users report a high rate of cigarette smoking compared to the general population (~70–80% vs. ~20–22%).[8–13] In cocaine users, Meier et al. reported a positive correlation between the severity of nicotine dependence as measured by the Fagerström Test of Nicotine Dependence (FTND) [14] and greater drug severity on the Addiction Severity Index.[15] Further, in cocaine users who were in treatment, higher FTND scores were associated with

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The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

more urine drug screens positive for cocaine in patients who were abstinent from cocaine at the start of treatment.[16] These results suggest that co-morbid nicotine dependence may relate to an increased risk of relapse after stopping use of stimulants like cocaine.

Clinical trials targeting cigarette smoking in cocaine-or opioid-dependent smokers have been less effective compared to those studies which enrolled smokers without co-morbid addictions.[17–22] These interventions have involved behavioral treatments (eg, supportive counseling, motivational interviewing, and contingency management) or behavioral treatment in conjunction with pharmacotherapy (ie, nicotine patch, nicotine gum, or bupropion). In general, these trials have shown modest or null findings in terms of cessation rates in this challenging population of smokers.

Preclinical studies have indicated a possible link between nicotine and cocaine addiction. Nicotine treatment induced self-administration of cocaine in rodents and facilitates relapse to cocaine.[23,24] Further, the nicotinic receptor antagonist mecamylamine decreased sensitivity to cocaine in a place preference paradigm[25] and decreased cocaine self-administration. These studies suggested that nicotinic receptors may play a role in maintenance of cocaine use behavior and treatments targeting nicotine receptors may have efficacy for the treatment of cocaine addiction.

Recently, varenicline (Chantix®) has been marketed as a pharmacological aid for smoking cessation.[26,27] Varenicline is a partial agonist at the $\alpha 4\beta 2$ nicotinic ACh receptors.[28] The $\alpha_4\beta_2$ nicotinic ACh receptors mediate the dopamine- releasing effects of nicotine in the nucleus accumbens, a key component of the reward circuit in the brain.[28] These findings suggest that varenicline may also be effective for the pharmacotherapy of cocaine addiction, although no previous studies examined varenicline's efficacy for cocaine addiction.

This pilot study has several main goals. The first was to determine safety and tolerability of varenicline in cocaine-and opioid-dependent smokers. This is especially important given varenicline's recent FDA mandated black box warning regarding mood changes and suicidality. While there has been ongoing evaluation of the safety and tolerability of varenicline in smokers, there has not been such an evaluation in an opioid-dependent cocaine-abusing sample. The second goal was to evaluate varenicline's efficacy for the treatment of cocaine abuse. As a third goal we examined varenicline's impact on smoking behavior in our subjects. We hypothesize that varenicline will be well-tolerated in our sample, and reduce cocaine use and smoking behavior.

METHOD

Participants

Thirty-one male and female treatment-seeking opioid-dependent subjects were recruited from the greater New Haven area for this study. To be considered for inclusion, subjects needed to meet a DSM-IV diagnosis of current opioid dependence and cocaine dependence or abuse, which was determined by a study physician and confirmed with the Structured Clinical Interview for DSM-IV (SCID). Additionally, subjects needed to have urine screen confirmation of recent cocaine and opioid use during the month prior to study entry. Subjects must also have smoked at least 10 cigarettes per day for at least 1 year. Women were included if they provided a negative urine pregnancy test at entry, agreed to use adequate birth control during the study, and agreed to take monthly urine pregnancy tests. Eligibility criteria were determined through an extensive medical evaluation, including blood work, electrocardiogram (ECG), urine analysis, urine toxicologies, medical, and psychiatric evaluation.

Subjects could be excluded from the study for a current diagnosis of alcohol, benzodiazepine, and other drug abuse or dependence (other than opioids, cocaine, and nicotine), ill health (eg, major cardiovascular, renal, endocrine, hepatic disorder), history of schizophrenia, or bipolar type I disorder, current use of over-the-counter or prescription psychoactive drugs (antidepressant, anxiolytics, antipsychotics, mood stabilizers, psychostimulants), and liver function tests results of greater than three times normal levels. Individuals with seizure disorder were also excluded. Subjects also needed to be able to read and understand the consent form. This study was approved by the West Haven VA Human Studies Subcommittee and the Yale University Human Investigations Committee. Subjects were not paid for their participation, but did receive free treatment.

Design and Procedure

This study was a 12-week randomized, double-blind, outpatient clinical trial in which 31 subjects were urn randomized into one of two treatment groups: Placebo or Varenicline (2 mg/day). Our computerized urn randomization was stratified based on age (35 or younger, 36 or older) or race (white, black, Hispanic, or other). Ultimately this randomization strategy led to five more subjects in the placebo condition with 18 placebo subjects versus 13 subjects for the varenicline group. Subjects attended clinic 6 days per week (Monday–Saturday) to complete weekly assessments, submit thrice weekly urine samples, and ingest study medication. On Saturdays, subjects received take home bottles of methadone and study medication to ingest on Sundays. Subjects were started on 30 mg of methadone during the first week and the dose was increased to reach 60 mg at the end of the first week. During the 12-week treatment phase, the dose of methadone was adjusted as needed with a maximum upper limit dose of 140 mg/day. During this first week all subjects also received a placebo pill, as the varenicline induction did not begin until Week 2.

During the second week of treatment, varenicline was administered to subjects randomized to the varenicline condition, with .5 mg/day during days 1–3 of Week 2, and .5 mg twice per day during days 4–7. Subjects received .5 mg at the dispensing window with their daily methadone dose and received .5 mg of varenicline for home self-administration later. During Week 2, placebo subjects received one placebo tablet at the window and one to take home. During Weeks 3–12, varenicline subjects received 1 mg twice daily. This was dispensed as 1 mg at the dispensing window along with methadone, and a 1 mg tablet to take home for self-administration later in the day. Subjects randomized to the placebo condition continued to receive one placebo tablet at the dispensing window with one to take home. To maintain the double-blind both the .5 mg and 1 mg doses of varenicline as well as the placebo pills were identical in appearance. The varenicline tablets were ground up by the West Haven VA pharmacy and then re-encapsulated, while the placebo capsules contained an identical appearing inert powder.

If a subject missed one dose, they were administered their usual dose if they came to the clinic the next day at their scheduled time. Subjects missing three consecutive doses were discharged from the study for noncompliance. In addition to receiving medication, each subject received weekly individual Cognitive Behavioral Therapy.[29] In these sessions, smoking behavior was not the primary outcome of interest and our counselors provided only the most minimal of smoking interventions, asking each subject weekly if they had chosen a stop date and reduced their smoking. Otherwise, each session was focused on opioid and cocaine use.

Assessments

All subjects received weekly interviews regarding the substances (including cigarettes) which they had used that week and the amounts. The SCID interview was given at intake to determine the presence of any DSM-IV mood or substance abuse disorder.[30] The Positive Affect Negative

Affect Schedule (PANAS)[31] was also given weekly to each subject. This 20-item inventory is the most frequently used instrument to assess positive and negative affective states. Subjects rate adjectives describing affective states on a scale of 1–5 using a specified time period (eg, now, today, past week, etc.). Scores are then added up to generate negative and positive scale scores. This scale is short, easy to administer, and has good psychometric properties.

The safety and tolerability of varenicline in a methadone-maintained subject group was evaluated by having the dispensing nurse ask each patient daily if they were experiencing any problems, whether the patient thought that they were related to the medication or not. Any adverse event would then be referred to the study physician for follow-up with the patient.

The severity of a subject's nicotine dependence was measured at baseline and weekly using the FTND.[32] In addition we gave each subject the Minnesota Nicotine Withdrawal Scale (MNWS)[33] weekly as well as the Brief Questionnaire on Smoking Urges (BQSU)[34] in order to assess each subject's degree of nicotine withdrawal and smoking urges.

Laboratory Tests

Urine samples were obtained thrice-weekly and analyzed for the presence of opioids and cocaine metabolites. This analysis was performed at the West Haven VA hospital laboratory using an Olympus AU 640 Emit system. The urine samples were rated as positive if the quantity of opioids or cocaine metabolite was greater than 300 ng/ml. Subjects were also given random breathalyzer tests. If the breath alcohol was >.00 and <.05, one-half the methadone dose was administered. In addition to these laboratory tests, subjects were evaluated weekly with a CO monitor (Vitalograph-BreathCO Monitor).

Data Analysis

The entire 31 subject intent-to-treat sample was used for statistical analysis. The baseline characteristics of subjects were compared using chi-square tests for categorical variables and a GLM ANOVA for continuous measures. Study retention across the two groups was evaluated using a Kaplan–Meier survival analysis, and a Cox regression when evaluating the predictive power of smoking on dropout status.

The primary outcome measures for this study were cocaine use and cigarette smoking. Cocaine use was measured by the thrice-weekly urine toxicology results. Cigarette smoking was assessed with a self-report of daily number of cigarettes smoked, verified with breath CO measurements.

We used the proportion of positive opiate and cocaine urine results per week for our analyses, for a total of 13 longitudinal results when including a baseline result (Week 0). For the primary smoking outcome we analyzed self-reported number of cigarettes used per week. These results were analyzed using Hierarchical Linear Modeling (HLM).[35,36]

To conduct these HLM analyses we used MIXOR, an HLM modeling program for ordinal outcome measures.[37] In MIXOR, estimates derived from the analysis are expressed as logits much as with logistic regression, and comparisons between models can be evaluated using overall log-likelihood statistics. We used all available data in our analyses, with no attempt made to interpolate missing data. HLM methodologies fit a regression line for each subject, effectively interpolating missing data, before deriving final estimates. Each HLM model included an intercept term, dummy-coded variables for the treatment groups, time, and treatment group by time interaction terms. The intercept term was treated as random, with all other effects specified as fixed.

Continuous outcomes were analyzed with a HLM methodology using a SPSS linear mixed model analysis. In these analyses, the intercept was treated as a random factor with all other factors fixed. For each outcome measure the covariance structure was inspected and multiple data runs were made with probable alternate covariance structures. The model having the lowest −2 log likelihood was retained as the analysis of best fit.

RESULTS

Baseline Characteristics, Treatment Retention, and Safety

The baseline subject characteristics are presented in Table 1. The 31 subjects used in this intent-to-treat analysis did not differ by any of these baseline measures when compared by medication condition. The placebo subjects for this study had a mean age of 34.4, with the varenicline subjects not significantly different (36.5 years). In addition, the placebo subjects did not differ from the varenicline subjects by either sex (78% vs. 85% male) or race (72% vs. 46% white). Of the 31 subjects, 58% smoked cocaine, 32% snorted cocaine, and 10% used IV cocaine.

The treatment retention for this study is presented in Fig. 1. There was no difference in the retention between the treatment groups over the course of the 12 weeks of the study (Log Rank $\chi^2 = 1.3$, $p < .26$). At Week 12, 78% of the placebo group was retained in treatment in comparison to 92% of the varenicline subjects. The mean number of cigarettes smoked in the baseline week was also evaluated as a potential predictor of dropout but this was also nonsignificant ($\chi^2 = .005$, $p < .95$).

None of our subjects experienced adverse events related to their participation in this study. The five subjects who dropped out of the study did so for a variety of reasons unrelated to adverse events including incarceration, too many missed medication doses, a request to transfer to a study that compensated subjects, and loss of transportation.

Cocaine and Opioid Use

Figure 2 shows the percent of urine toxicologies which were positive for cocaine across the 12 weeks of the study. The HLM analysis of these results did not indicate that varenicline reduced cocaine use over the course of 12 weeks for either group (placebo: $Z = 1.01$, $p < .31$; varenicline: $Z = .78$, $p < .44$). Additionally, the slopes for the two treatment groups did not differ from each other ($Z = .20$, $p < .84$).

Figure 3 presents the percent of positive opioid urine toxicologies. The placebo group significantly reduced their opioid use over 12 weeks (placebo: $Z = -3.83$, $p < .0001$) with a trend in the varenicline group indicating a reduction also ($Z = -1.91$, $p < .06$). However, there was no differential effect of treatment condition on this outcome ($Z = -1.29$, $p < .20$).

Smoking Behavior

In order to enter this study, subjects needed to have smoked at least 10 cigarettes per day for the past year. Figure 4 presents the mean self-reported number of cigarettes smoked per day across the 12-week trial. The placebo group did show some significant but modest reductions in daily cigarette use while in treatment ($F = 4.62$, $p < .03$), while the subjects treated with varenicline showed much steeper reductions in cigarette use ($F = 55.7$, $p < .0001$) with the rate of decrease being significantly different from that of placebo ($F = 16.5$, $p < .0001$). Overall the placebo group reduced their mean daily cigarette usage 8.01% compared to the varenicline group's 52.8% reduction. Despite these reductions only 1 placebo subject and 2 varenicline subjects reported having smoked no cigarettes during the last week of the study.

These self-report cigarette smoking data were verified with breath CO measurements. Smoking abstinence was based on expired carbon monoxide (CO < 8 ppm), obtained once weekly. At baseline, the two groups did not significantly differ in CO measurement, 27.8% of the placebo versus 30.8% of the varenicline group less than 8 ppm (χ^2 = .03, Fishers exact p = 1.0). Over the course of the study, however, the varenicline group obtained significantly more weeks that subject's CO measurements were 8 ppm or below compared with the placebo group when using the entire intention-to-treat sample (placebo 21% vs. varenicline 46.1%; χ^2 = 26.37, Fisher's exact p < .0001). In order to eliminate the possibility that these results were due to differential dropout from the study, the analysis was redone using only subjects who completed the entire trial. The results of this analysis was also significant with subjects treated with varenicline having significantly more weeks being rated as engaging in nonsmoking behavior when compared to those receiving placebo (44.2% vs. 14.8%; χ^2 = 35.69, Fisher's exact p < .0001).

Additionally, the FTND scores for the two medication groups showed a similar pattern of results (Fig. 5). The FTND scores for the placebo group did not change significantly while in treatment (Z = −1.15, p < .25), while the FTND scores for the varenicline group showed significant reductions across 12 weeks (Z = −7.38, p < .000001) with a highly significant difference in slopes between the two groups (Z = 3.35, p < .0008).

An analysis of the BQSU Total Score (Fig. 6) showed reductions in smoking urges for both treatment groups (placebo: F = 13.59, p < .0001; varenicline: F = 12.53, p < .002), with no differences in this rate of improvement between the groups (F = .35, p < .56). Similar findings were observed for Factor 1 (anticipation that smoking will produce pleasure) and Factor 2 (anticipation of relief from negative affect) of the BQSU, with no significant treatment effects (p > .05).

Figure 7 presents data from the MNWS. Both treatment groups significantly reduced their MNWS total score across the 12 weeks (placebo: F = 23.62, p < .0001; varenicline: F = 20.15, p < .0001). The rate of these reductions did not differ between the placebo and varenicline groups, however (F = .001, p < .97).

Affect

On the negative scale of the PANAS (Fig. 8), both treatment groups showed reductions over time (placebo: F = 4.36, p < .04; varenicline F = 16.04, p < .0001), but neither slope differed from the other (F = 2.43, p < .12). The varenicline medication group showed significant reductions across the 12 weeks on the positive scale of the PANAS (F = 13.05, p < .0001), while subjects in the placebo condition showed no changes in the positive scale over time (F = 1.34, p < .25). These slopes over 12 weeks for the two treatment conditions differ significantly (F = 4.72, p < .03). Given the substantial differences in SCID rated lifetime depression between the varenicline and placebo groups we conducted another analysis utilizing the lifetime depression diagnosis as a covariate in the positive subscale analysis. This second model including the SCID lifetime depression diagnosis was a significant improvement over the model without the depression diagnosis (χ^2 = 5.622, p < .02). These results indicate that the difference in PANAS positive scores is not significant after adjusting for lifetime depression (F = 1.116, p < .65).

DISCUSSION

To our knowledge, this is the first report of a clinical trial using varenicline for the treatment of cocaine dependence in methadone-maintained subjects. During postmarketing use of varenicline, depressed mood, agitation, changes in behavior, suicidal ideation, and suicide have occurred in patients attempting to quit smoking while taking varenicline. Based on these reports, the Food and Drug Administration (FDA) recommends that patients should be

monitored for any behavioral or mood changes (aggressive or erratic behavior) or suicidal thoughts while taking varenicline (US FDA, 2007). Due to these new FDA warnings, it was of clinical interest to evaluate the safety and tolerability of varenicline in our subject population. The subjects in this study did not experience any adverse events related to the medications given in this study and were retained in the study at rates comparable to those for placebo. Varenicline treatment was not associated with any increases in negative affect, measured with the PANAS. We did observe a significant decrease in the positive scale of the PANAS in the varenicline group compared to the placebo group, although this appears to be the result of randomization differences in lifetime depression. The significance of this reduction in positive affect remains to be determined. Overall, these results support the safety and tolerability of varenicline in cocaine using smokers maintained on methadone.

In addition to this safety data, our study also provides potential efficacy data for smoking behavior. Subjects who were assigned to varenicline reported greater reduction in self-report smoking and these findings were corroborated with breath CO measurements. Additional support for these smoking-related findings is found in the FTND, where the varenicline subjects again evidenced lower scores across time for the varenicline subjects when compared to the placebo group. By the end of the trial, the varenicline subjects had cut the number of cigarettes they smoked per day by over half. These findings are important since reductions in smoking behavior took place even though the subjects received only the most minimal of encouragement to stop smoking. This intervention occurred in the counseling session where each patient would be asked if they picked a quit date and stopped smoking yet. Further, as mentioned earlier, cocaine-using smokers and smokers maintained on methadone have typically been resistant to smoking cessation treatments.[17–22] Effective treatments for smoking cessation in this group will have important clinical implications.

Given the smoking reductions seen in the varenicline group in comparison to the placebo group, it is interesting that there were equal overall reductions for scores on the MNWS and BQSU for both treatment groups. One explanation may be that many of the items on these inventories correlate highly with opioid withdrawal symptoms (eg, irritability, anxiety, difficulty concentrating, restlessness, depression). As patients are stabilized on methadone we might reasonably expect reductions on these measures for all patients entering treatment.

Unfortunately we did not find evidence that varenicline was effective in reducing cocaine use. This either may be due to the small number of subjects used in this pilot study, or to a genuine lack of effect. Larger clinical trials will be needed to conclusively determine whether varenicline is effective in reducing cocaine use in opioid-dependent subjects.

The main limitation of this study was the small sample size, especially for the efficacy outcomes. However, we felt it was important to conduct a pilot study to evaluate the efficacy of varenicline for reducing cocaine use in our study sample. Second, the study did not measure cotinine levels as a biochemical measure of cigarette smoking, or include more frequent monitoring of CO levels. Cotinine levels would have complemented the self-report smoking and breath CO measurements in assessing changes in cigarette smoking levels. In addition, it is unclear to what degree subjects were motivated to stop smoking and whether this motivation was equal across the treatment groups. Future studies may wish to include a motivational measure to address this issue. In spite of these limitations, this pilot study provides important information regarding the safety and potential efficacy in this sample.

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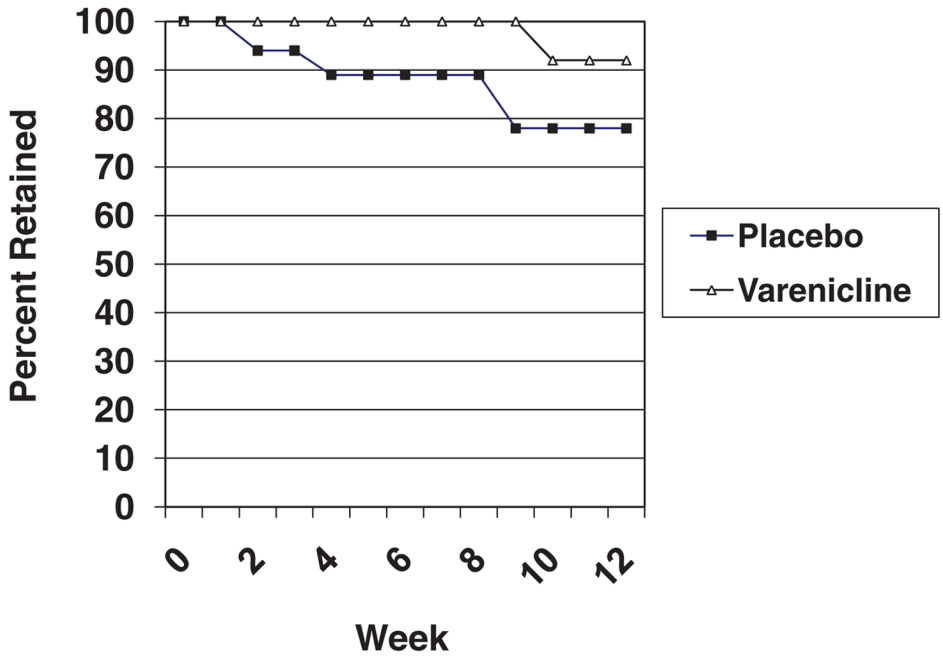

FIGURE 1.
Subject retention across 12 weeks by medication condition. The two treatment groups did not differ in retention (log rank $\chi^2 = 1.3$, $p < 0.26$).

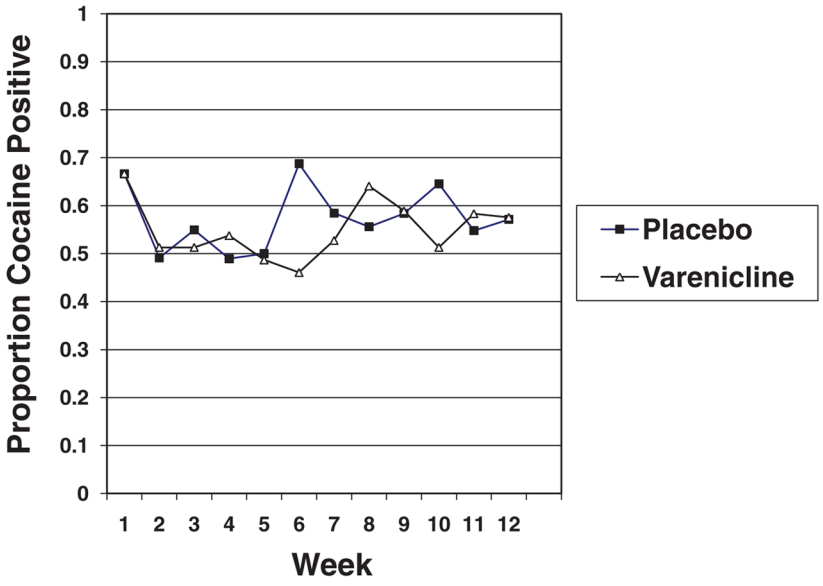

FIGURE 2.

Proportion of cocaine positive urine results by medication condition and week. There are no significant changes in slope for either group and these slopes do not differ from each other ($Z = 0.20$, $p < 0.84$).

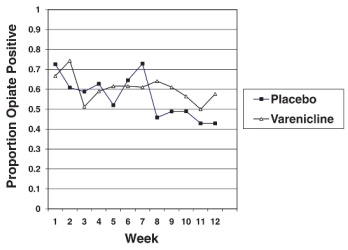

FIGURE 3.

Proportion of opioid positive urine results by medication condition and week. Both the placebo and varenicline groups reduced their opioid use across 12-weeks, but there was no differential effect of treatment condition ($Z = -1.29$, $p < 0.20$).

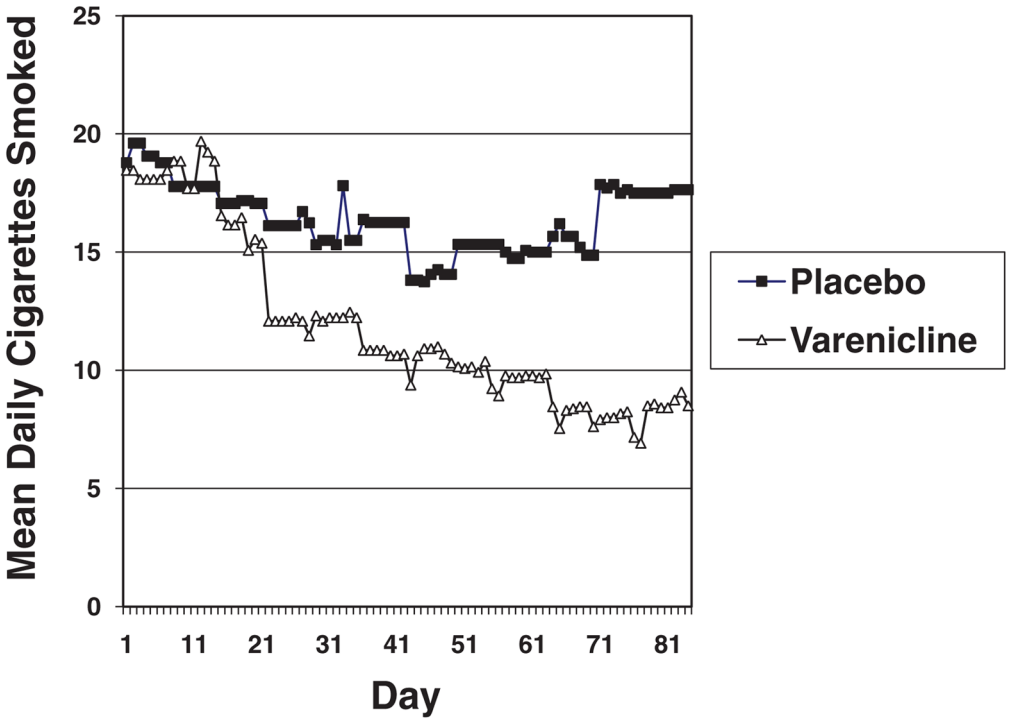

FIGURE 4.

Mean self-reported number of cigarettes smoked per day by medication condition. Includes only subjects who smoked while in treatment (one subject excluded). An autoregressive 1 (AR1) covariance structure provided the best fit to the model. Both treatment groups reduced the mean number of cigarettes smoked per week, but the varenicline group's reductions were significantly greater when compared to placebo ($F = 16.5$, $p < 0.0001$).

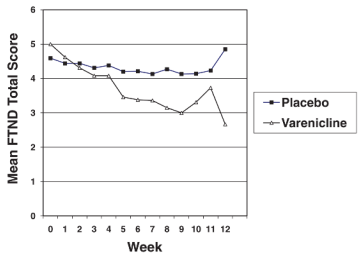

FIGURE 5.

Fagerström mean weekly total score by medication condition. The results show that the placebo group did not change over 12 weeks. The varenicline group showed significant reductions across 12 weeks ($Z = -7.38$, $p < 0.000001$) with a highly significant difference in slopes between the two groups ($Z = 3.35$, $p < 0.0008$).

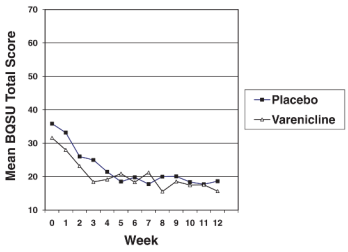

FIGURE 6.

Brief Questionnaire of Smoking Urges Total Score across 12 weeks by medication group. Heterogeneous Toeplitz covariance structure provided the best model fit. Both groups significantly reduced their smoking urges while in treatment but did not differ from each other ($F = 0.35$, $p < 0.56$). BQSU scores can range from 10 to 70.

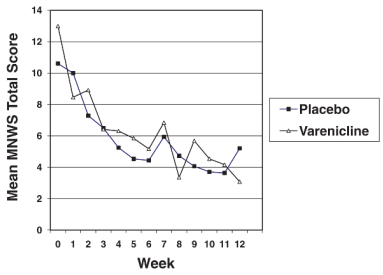

FIGURE 7.

Minnesota Nicotine Withdrawal Scale (MNWS) Total Score across 12 weeks by medication group (Heterogeneous AR1 covariance structure). Both groups significantly reduced their nicotine withdrawal scores while in treatment and these reductions did not differ from each other in slope ($F = 0.001$, $p < 0.97$). MNWS scores can range from 0 to 32.

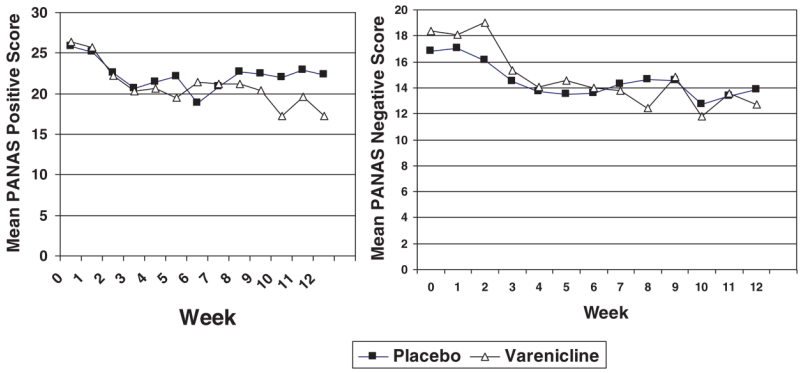

FIGURE 8.

PANAS positive scale total by med code and week: Heterogeneous AR1 covariance structure used. The placebo group showed no difference on the positive scale of the PANAS, while the varenicline group showed a reduction over time ($F = 13.05$, $p < 0.0001$). This difference in slopes for the placebo vs. varenicline groups is significant ($F = 2.43$, $p < 0.12$). PANAS negative scale total by Medication Condition and Week: Heterogeneous AR1 covariance structure used. Both treatment groups showed significant reductions in the PANAS negative scale over time, but this rate of reduction did not differ between the two groups ($F = 2.43$, $p < 0.12$). The PANAS subscale scores range from 10 to 50.

TABLE 1

Subject baseline demographics by medication condition

Baseline measure	Placebo (*n* = 18)	Varenicline (*n* = 13)
Age-years (SD)	34.4(12)	36.5(12)
Sex (no. of male/female)	14/4	11/2
Race (no. of C/AA/H/Oth)*	13/4/0/1	6/3/4/0
Education (years)†	12.8	12.7
Net income ($/month)‡	1,522	1,351
Lifetime heroin use (years)	6.8	9.4
Lifetime cocaine use (years)	7	10.9
Heroin use (no. of days/month)§	15.4	12.2
Cocaine use (no. of days/month)§	10.9	11.5
Alcohol use (no. of days/month)§	1.1	0.6
SCID Opiate Dependence-Life (%)	100	100
SCID Cocaine Dependence-Life (%)	94.4	84.6
SCID Major Dep. Dependence-Life (%)	11.1	30.8
Panas Positive Affect score	25.8	26.4
Panas Negative Affect score	16.8	18.4
Fagerström Test of Nicotine Dependence (FTND)	4.7	5.0
Nicotine Withdrawal Symptom Checklist	10.6	13.0
BQSU—Total	35.8	31.6
BQSU—Positive Total	22.1	18.4
BQSU—Negative Total	10.3	9.8
Mean cigarettes smoked per day	19.1	18.2
Carbon monoxide (ppm)	17.2	10.1

Note: All treatment group differences are nonsignificant.

*Race: C, Caucasian; AA, African-American; H, Hispanic; Oth, Other;

†Education: years;

‡Net income ($/month)—dollars earned in the month prior to study entry;

§No. of days/month—number of days used substance in the month prior to treatment entry.