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Toward Personalized Smoking-Cessation Treatment: Using a Predictive Modeling Approach to Guide Decisions Regarding Stimulant Medication Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in Smokers

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Abstract

Background and Objectives—Osmotic-release oral system methylphenidate (OROS-MPH) did not show overall benefit as an adjunct smoking cessation treatment for adult smokers with ADHD in a randomized, placebo-controlled, multicenter clinical trial. A secondary analysis revealed a significant interaction between ADHD symptom severity and treatment-response to OROS-MPH, but did not account for other baseline covariates or estimate the magnitude of improvement in outcome if treatment were optimized. This present study addressed the gaps in how this relationship should inform clinical practice.

Methods—Using data from the Adult Smokers with ADHD Trial ($N = 255$, six sites in five US States), we build predictive models to calculate the probability of achieving prolonged abstinence, verified by self-report, and expired carbon monoxide measurement. We evaluate the potential improvement in achieving prolonged abstinence with and without stratification on baseline ADHD severity.

Results—Predictive modeling demonstrates that the interaction between baseline ADHD severity and treatment group is not affected by adjusting for other baseline covariates. A clinical trial simulation shows that giving OROS-MPH to patients with baseline Adult ADHD Symptom Rating Scale (ADHD-RS) >35 and placebo to those with ADHD-RS ≤ 35 would significantly improve the prolonged abstinence rate ($52 \pm 8\%$ vs. $42 \pm 5\%$, $p < .001$).

Conclusions and Scientific Significance—In smokers with ADHD, utilization of a simple decision rule that stratifies patients based on baseline ADHD severity can enhance overall

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Declarations of Interest

The other authors have no competing interests to declare.

achievement of prolonged smoking abstinence. Similar analysis methods should be considered for future clinical trials for other substance use disorders.

INTRODUCTION

Effective smoking cessation treatment requires simultaneous treatment of nicotine dependence and comorbid psychiatric conditions, such as attention-deficit hyperactivity disorder (ADHD).¹ A number of studies^{2,3} suggest that in children and adults with ADHD, cigarette smoking is both more common and more difficult to treat. Furthermore, several nicotinic agents are being evaluated for the pharmacotherapy of ADHD.⁴⁻⁷ These observations suggest that cigarette smoking and ADHD symptoms may have common underlying etiologies.

While a substantial body of evidence suggests that psychostimulants are safe and effective for treating ADHD,^{8,9} there is no compelling evidence for their efficacy in treating nicotine dependence. Similarly, while nicotine replacement therapy is effective in facilitating smoking cessation, there is little evidence that it alone can adequately treat core ADHD symptoms, such as poor response inhibition, that may be causally linked to the maintenance of nicotine dependence.¹⁰ A multicenter, randomized, double-blind, placebo-controlled trial was conducted in the National Drug Abuse Treatment Clinical Trials Network (CTN) (Adult Smokers with ADHD Trial, CTN-0029) to test the hypothesis that combining osmotic-release oral formulation methylphenidate (OROS-MPH) and nicotine patch would enhance rates of prolonged abstinence from nicotine.¹¹ The pre-specified primary outcome analysis showed that while pharmacologic treatment resulted in a significant reduction of ADHD severity, smoking abstinence rates did not differ significantly between OROS-MPH and placebo groups. Subsequent subgroup analyses showed significant heterogeneity in treatment effects with respect to study site (participants enrolled at tobacco dependence clinics achieved abstinence more frequently than those enrolled in general community or ADHD clinics),¹² ADHD subtype (OROS-MPH was more effective than placebo in participants with the combined subtype),¹³ ethnicity (OROS-MPH was more effective among non-whites),¹⁴ and importantly, baseline ADHD symptom severity (OROS-MPH was more effective than placebo for participants with higher baseline severity, but *less* effective than placebo in those with lower baseline severity).¹⁵ Laboratory studies measuring the effects of psychostimulants on tobacco withdrawal and craving have also yielded inconsistent results: while methylphenidate might improve withdrawal symptoms in smokers who wished and made an effort to stop smoking,¹⁶ it increased the total number of cigarettes smoked and the total number of puffs in subjects recruited without considering their desire to stop smoking.¹⁷ This difference in motivation could potentially explain the inconsistencies in the results. We also note that in the CTN-0029 trial, the total number of cigarettes smoked per day was reduced by OROS-MPH, despite a lack of difference in the rate of attaining prolonged abstinence.¹¹ These results, taken together, suggest that the overall lack of efficacy of OROS-MPH as an adjunct treatment for smoking cessation may be due to complex underlying treatment heterogeneities.

A number of studies have examined patient characteristics as predictors of treatment responses in smoking cessation: for instance, male smokers have better response to nicotine

replacement therapy¹⁸; select genetic loci¹⁹ and clinical predictors²⁰ have been identified for bupropion; high-dose nicotine replacement may be more effective for heavy smokers.²¹ Nicotine metabolism rate^{22,23} and several pharmacogenomics and neuroimaging biomarkers are currently being evaluated.²⁴ Nevertheless, few studies directly examine the clinical utility and effect size of optimizing treatments based on patient characteristics—“precision medicine”—in smoking cessation treatment. How to use these patient characteristics clinically and the degree to which they will improve treatment outcomes remain unclear.

We hypothesize that baseline ADHD severity is a clinically relevant patient characteristic for optimizing treatment at an individual level. We want to estimate the threshold of baseline ADHD severity for clinicians to decide between OROS-MPH and placebo. We also want to calculate the magnitude of improvement in clinical outcome with optimal treatment. We utilized a clinical trial simulation analysis with predictive models²⁵ to test these hypotheses. In standard subgroup analyses, strengths of associations are reported in measures, such as odds ratios, that are difficult to interpret and use clinically. Our approach has the distinct advantage of being able to quantify directly the effect of implementing a pragmatic clinical practice algorithm.

METHODS

Participants

Participants in this study were 255 adults with a DSM-IV diagnosis of ADHD. Six study sites located in Massachusetts, Ohio, New York (two sites), Oregon, and Minnesota recruited participants. Two study sites were substance abuse community treatment programs; two were ADHD clinics and two smoking cessation clinics. The main inclusion criteria were: healthy adult subjects in good physical health, smoking at least 10 cigarettes daily, 18–55 years old (older patients excluded for difficulty in recalling childhood ADHD symptoms), meeting DSM-IV criteria for ADHD as assessed by the Adult Clinical Diagnostic Scale version 1.2²⁶ and having an ADHD Symptoms Rating Scale²⁷ (ADHD-RS) score >22. Main exclusion criteria included any significant risk for suicide or homicide, use of other tobacco products, a positive urine test for illicit substances, other major psychiatric diagnoses or substance use disorders such as psychosis, bipolar disorder or current major depression, and current treatment for ADHD or nicotine dependence; for women, pregnancy, breastfeeding, or unwillingness to use adequate birth control. All participants provided informed consent, and the study was reviewed and approved by the Institutional Review Boards at the participating sites.

Assessments

The main outcome for the present analysis was prolonged abstinence, defined as self-report of tobacco abstinence without treatment failure (smoking each day for seven consecutive days or having smoked at least one day of each week in two consecutive weeks) during study weeks 7–10, using recommendations²⁸ from the Society for Research on Nicotine and Tobacco and FDA standards for approving smoking cessation medications. While there are other clinical assessment metrics, such as the Russell Standard,²⁹ in this study we focus on the ability to achieve abstinence immediately after treatment as opposed to intermediate to

longer term outcome. These measures were obtained weekly using timeline follow-back method, which assessed the use of tobacco day by day prior to the follow-up date^{30,31} and verified biochemically by expired carbon monoxide <8 ppm. A secondary outcome measure was complete abstinence (no slips or lapses) during weeks 7–10.

The covariates tested in the analysis included age, sex, race/ethnicity, desire to smoke (also known as craving), baseline ADHD-RS, the Minnesota Nicotine Withdrawal Symptoms Scale (MNWS), Fagerstrom Test for Nicotine Dependence score,³² baseline Beck Depression Inventory (BDI),³³ lifetime major depression, marital status, education level (in years), and site type (substance abuse community treatment programs, tobacco dependence clinic or ADHD clinic). To avoid possible multicollinearity, ADHD subtype was not included because it was shown to be highly correlated to symptom severity measured by ADHD-RS.³⁴ While weekly values for time varying covariates were available during the trial, we restricted our present analysis to the measured baseline covariates (ie, at the start of the trial prior to quitting), as the goal was to develop a predictive model that could be used prior to the initiation of OROS-MPH treatment.

Procedures

Details of the study procedures were described elsewhere.¹¹ Briefly, the study was an 11-week, double-blind, placebo-controlled, parallel-group trial of OROS-MPH versus placebo, plus brief weekly individual smoking cessation counseling for 11 weeks and 21 mg/day nicotine patches given at the smoking quit day (day 27), free of charge. OROS-MPH was titrated to a maximum of 72 mg/day over the first 2 weeks and continued at the maximum tolerated dose until the end of the active treatment period (week 11). Randomization was in a 1:1 ratio, stratified by site, and completed by computer at a centralized location. Participants were compensated for their time at a rate of \$25 per study visit (with the exception of a \$50 payment at the week 11 study visit due to the higher assessment burden). Brief, manual-guided counseling (10 min/week) was delivered based on an evidenced-based program for effective tobacco cessation.³⁵

Statistical Analysis

Overview—Our predictive models were generalized linear models (GLMs). Binary outcomes (prolonged abstinence) resulted in logistic regression models. GLMs were fitted using Iteratively Reweighted Least Squares (IRLS) for maximum likelihood. All predictive modeling and clinical trial simulation analyses were carried out in MATLAB and R, using the Statistics Toolbox. Missing data were imputed using multiple imputations for baseline covariates; for smoking cessation outcome, missing days were coded as smoking days.¹¹

Exploring the Interaction Between Baseline Covariates and ADHD-RS—We first pared down baseline covariates of interest in a hypothesis driven approach by only examining covariates that were known to be significantly related to baseline ADHD severity.¹⁵ We excluded covariates that cannot be measured and recorded as part of routine clinical practice. We explored whether the treatment by ADHD-RS interaction could be accounted for by adjusting for main and interaction effects for a covariate using the following models:

Prolonged Abstinence ~ TREATMENT + ADHD-RS + COVARIATE + (BETA)
TREATMENT * ADHD-RS (Model 1)

Prolonged Abstinence ~ TREATMENT + ADHD-RS + (BETA1) COVARIATE +
TREATMENT * ADHD-RS + (BETA2) TREATMENT * COVARIATE (Model 2)

Each of the 11 covariates was used once (22 models). We calculated regression coefficients of the interaction terms to explore possible treatment interaction effects.

Evaluating Predictive Model Performance—We evaluated the performances of the predictive models with and with out ADHD-RS * TREATMENT interaction term explicitly using cross-validation: a subset of the sample was used for model fitting (training set), and an independent subset was used for performance evaluation (testing set). More specifically, we used K -fold cross-validation ($K = 10$) and Receiver Operating Characteristic (ROC) analysis to evaluate the performance of the model. Each model yielded an ROC curve and an Area Under the Curve (AUC) value, a threshold-independent measure of model accuracy. We also evaluated a complex model with all treatment-by-covariate interactions and covariate-by-covariate interactions using regularized regression with LASSO to automatically decrease the sizes of the regression coefficients. (For further details on modeling and statistical methodology, please contact the author directly for electronic supplementary material).

Estimating the Clinical Utility of the Predictive Model—To estimate the improvement in clinical outcome with treatment stratification, we calculated the probability of achieving prolonged abstinence at a variety of different levels of baseline ADHD severity. Using the same cross-validation procedure above (K -fold), we divided the sample into random subsamples of training and testing sets. We first fit the predictive model on the training set and calculated the probability of achieving prolonged abstinence for the testing set at specific baseline ADHD severity. This procedure allowed for visualization of differential treatment effect as a continuous function of baseline ADHD severity (Fig. 1). We then used the same testing set sample and flipped the treatment group assignment from what was originally assigned, and estimated the probability of achieving prolonged abstinence if the participant in the testing set was given a different treatment (ie, placebo instead of OROS-MPH or vice versa.) These predicted probability values, along with the actual outcome at the end of the study, allowed us to conduct a clinical trial simulation analysis (Fig. 2a, further explanations in the results section below): randomizing patients to either random treatment assignment or an intervention of using a clinical decision rule based on stratification of baseline ADHD severity. This analysis realistically estimated the outcome in a sequential randomization design where the first stage of the trial (ie, the original trial, but only for the training set) was used to select interventions for randomization (stratified assignment vs. random assignment) in the second stage.

Results

Exploring the Interaction Between Baseline Covariates and ADHD-RS

There was no evidence of statistically significant differences in baseline covariates between OROS-MPH and placebo groups (results not shown, available as a supplementary upon request). The significant treatment-by-baseline ADHD-RS interaction effect remained significant in all models with the addition of any one of 11 covariates and its interaction with treatment (results not shown, available as a supplementary upon request). The size of the coefficient for this interaction was not changed when adjusted for another baseline covariate. None of the other baseline covariate (BETA1) or covariate and treatment group interaction (TREATMENT * COVARIATE, BETA2) terms had a significant coefficient, suggesting that these terms did not contribute significantly over and above the baseline ADHD-RS by treatment interaction. Similar patterns were seen for complete abstinence (data not shown).

Performance of the Predictive Models

The exploratory analysis suggested that adding additional COVARIATE or TREATMENT * COVARIATE interaction terms may not improve predictive performance. To test this, we constructed predictive models with and without these predictors (Table 1). We compared the null model (Prolonged Abstinence ~ TREATMENT + ADHD-RS) to the other models, and found that adding the TREATMENT * ADHD-RS interaction improved the predictive performance significantly (Fig. 3), while the addition of other baseline covariates did not. Adding the COVARIATE * TREATMENT interactions also did not improve model performance (data not shown). A model that incorporated all covariates and TREATMENT * COVARIATE and COVARIATE * COVARIATE interaction terms simultaneously using regularized regression showed no overall improvement in performance. While overall there was no performance improvement, we also estimated an optimistic metric of performance improvement: was the performance better for a small set of patients for whom this complex model was most confident about (ie, with a probability of achieving or failing to achieve prolonged abstinence >0.9)? For this subset, the regularized regression model showed only a modest improvement (Table 1, Fig. 3a, b): even with the most optimistic restrictions, in a 255 patient sample, the most complex model made correct predictions for an additional 10–20 patients. Nevertheless, this improvement of the predictive performance was statistically significant, corrected for multiple comparisons (Fig. 3b, Kruskal–Wallis, $p < 1E-3$). Changing the outcome of prediction from prolonged abstinence to complete abstinence did not appear to change the best predictive performance of the models tested.

Estimating Clinical Improvement

The most parsimonious predictive model (Prolonged Abstinence ~ TREATMENT + ADHD-RS + TREATMENT * ADHD-RS) yielded a moderate degree of predictive performance, approximately correct about 60% of the time for any given patient. This model was therefore not useful for predicting an individual outcome. Nevertheless, it could be used to estimate the overall improvement of outcome if the key predictor, baseline ADHD severity, was correctly stratified. Proper stratification required estimation of the appropriate threshold for treatment. We first estimated the probability of achieving prolonged abstinence for the trial enrollees if they were uniformly given either placebo or OROS-MPH. As shown

in Fig. 1, the estimated probability of achieving prolonged abstinence was different for patients across the entire range of baseline ADHD-RS, confirming and extending previous findings, with OROS-MPH superior to placebo when baseline ADHD-RS >36 , inferior when baseline ADHD-RS <35 , and equivalent when baseline ADHD-RS between 35 and 36. The estimates of probability of achieving prolonged abstinence had a mean and a variance, as visualized in the box plots at each level of baseline ADHD severity. In K -fold cross-validation, any statistically estimated value depended on the subsample that was chosen as the training set. As K subsamples were rotated as the training set, there were in total K estimates. We tested the hypothesis that using this particular cross-validation scheme, there was a statistically significant difference in probability of achieving prolonged abstinence at each of the baseline ADHD-RS level (31 tests). Other than ADHD-RS = 36, which gives a $p = .66$, at all other ADHD-RS levels, $p < .001$ (two tailed t -test, with Bonferroni correction).

To estimate the effect of treatment stratification, we calculated the overall improvement of clinical outcome by simulating a new clinical trial, randomizing participants to either random treatment assignment or stratified treatment assignment (Fig. 2a). We simulated a new trial in which we divided the testing set into either “treatment as usual” which consisted of randomizing participants to either placebo or OROS-MPH according to their original treatment assignment, or “active intervention”, which consisted of an additional step of estimating what the optimal treatment would be, then pooling outcomes for the participants who received the optimal treatment during the original trial. We identified the optimal treatment (ie, OROS-MPH or placebo) by either using the best performing predictive model as above (calculate an exact probability of achieving prolonged abstinence, and assign the treatment that maximizes that probability), or further simplifying the optimal treatment rule: OROS-MPH for every patient with baseline ADHD-RS >35 , and placebo for those with baseline ADHD-RS ≤ 35 . The randomized treatment assignment group (GROUP C) had an average rate of achieving prolonged abstinence of 0.42 (STD = 0.03), which was the same as the previously reported rate for the entire trial (0.42). The average rate of achieving prolonged abstinence for the group with proper stratification using the most parsimonious predictive model (GROUP A) was 0.49 (STD = 0.04). The average was 0.52 (STD = 0.03) using the simplified stratification rule (OROS-MPH for only baseline ADHD-RS >35). These average rates of achieving prolonged abstinence for Group A were significantly greater than the rate for the group with random assignment, adjusting for multiple comparisons ($p < 1E-3$, Bonferroni correction). Finally, we found that the group where reverse stratification was done (GROUP B, ie, OROS-MPH for low severity group, placebo for high severity group) had a decreased average prolonged abstinence rate of 0.35 (STD = 0.04, $p < 1E-3$, Bonferroni correction). The simplified stratification rule slightly outperformed the rule based on the most parsimonious predictive model, implying a degree of robustness in our extrapolated threshold of treatment equivalence at ADHD-RS = 35, though this small improvement was not significant after adjusting for multiple comparisons.

Discussion

In the present study, we built predictive models using the CTN Adult Smokers with ADHD trial data.¹¹ Predictive modeling demonstrated that the significant effect of the interaction

between baseline ADHD severity and treatment group assignment on prolonged abstinence was not affected by adjusting for other baseline covariates and their interactions with treatment. It also showed that OROS-MPH would likely be more beneficial for improving prolonged abstinence as baseline ADHD increases, and more harmful as baseline ADHD severity decreases, with an estimated benefit-to-harm crossover at ADHD-RS = 35. Using a simulated clinical trial analysis, we estimated the magnitude of improvement of clinical outcome (52% vs. 42% in rate of achieving prolonged abstinence) with optimal treatment and argued that baseline ADHD-RS would therefore be a clinically useful patient characteristic for treatment optimization.

This is one of the very few studies in literature in which the degree of improvement of smoking cessation outcome, through implementation of patient stratification, is directly estimated. From a methodological perspective, clinicians have long argued that personalizing treatment improves outcome based on intuition and experience, but such an optimal treatment rule is rarely rigorously defined and the possible effect on clinical outcome is difficult to evaluate using traditional subgroup analysis. In traditional subgroup analyses, measures of subgroup effects are expressed in odds ratios and other quantities that are difficult to translate into clinical practice.³⁶ Our approach, on the other hand, directly produces estimates of clinical outcome when different clinical decision rules are implemented. In our study, the predictive performance itself is modest (~60% correct), and the only variable used in personalization is baseline ADHD severity—the other covariates do not affect predictive performance. Adding more covariates and making the model more complex may improve prediction in a small number of patients, as shown by our analysis using LASSO regression, but this effect is likely not clinically significant. This suggests that even with a relatively large sample size, it is difficult to confidently predict the eventual outcome for an individual patient. However, our study shows that in these circumstances, clinical trial simulation, used in conjunction with predictive modeling, as a methodological strategy recently made possible with increasing computational capacity, may be especially useful. Our strategy can extract group-level effects of implementing specific clinical decision rules, which may derive from multiple, possibly competing treatment-by-covariate interactions.

The present analysis reveals the limitations in estimating individual treatment outcome using baseline covariates. Correlations between baseline covariates and prolonged abstinence may be mediated through their effects on baseline ADHD severity, and therefore do not represent independent sources of predictive information: ADHD subtype, which is excluded in our analysis, is an example of a covariate that exhibits such correlations. Patients with the combined subtype, by definition, experience more symptoms and therefore have a higher baseline severity. Secondly, baseline characteristics may influence outcome, but this influence may be too small, or not interacting with treatment, and therefore cannot add much to a model that explicitly aims to optimize outcome through optimizing medication. Finally, *unmeasured* baseline characteristics may influence outcome and interact with treatment group assignment. Our analysis suggests, nevertheless, that without knowing all of the covariates and the complex correlational relationship between covariates and outcome, personalizing treatment based on baseline ADHD symptom severity alone can significantly

improve clinical outcome over randomized assignment. These results also further argue for the importance of routine dissection of baseline severity by treatment interaction as an important part of clinical trial analysis.³⁷

Clinically, for patients who want to quit smoking and have a baseline ADHD-RS >35, OROS-MPH should simultaneously reduce ADHD symptoms and promote prolonged abstinence from nicotine. For patients who have a baseline ADHD-RS ≤35, OROS-MPH treatment may make smoking cessation more difficult—a risk that needs to be balanced with the benefit of improved ADHD symptoms. One potential future study would be another randomized trial with these adaptive parameters³⁸ such as an adaptive optimal dose-finding study. Another possibility is to use our results to carry out evidence-based quality improvement and implementation projects, especially in large managed care settings, to measure the improvement in clinical outcome, and assess whether the improvement in outcome matches our estimates. For instance, the estimates of probability of achieving prolonged abstinence in Fig. 2 are extracted and interpolated through repeated resampling of this large clinical trial data set. Clinicians can therefore use this figure during the evidence-based informed consent process, before starting psychostimulants, as a visual aid: a more intuitive explanation of the potential advantages of medication for patients with more severe ADHD symptoms who also smoke. These interventions may be effective both in improving medication compliance and in assisting in smoking cessation.

There are several limitations in the present study. By design, we included only baseline predictor variables: clinicians can most readily apply the stratification rule at the initial evaluation. However, whether a particular patient will quit smoking likely involves factors not measured or measurable at the start of the trial. For instance, early response in the first few weeks correlates with ultimately achieving abstinence in a number of treatment studies of substance use disorders.^{39,40} Predictive models that incorporate early treatment response might therefore be useful in making a decision in giving up the current treatment and trying something new. Secondly, the inclusion criteria of the trial are stringent in excluding older patients for difficulty in accurately diagnosing ADHD, as well patients with significant other co-morbid psychiatric or substance use disorders. Data from a future larger effectiveness trial can allow for predictive models that are more generalizable. Another limitation is the deliberate lack of consideration of casual mechanisms. Future studies will systematically analyze the casual factors in mediating the interaction effects of baseline ADHD severity, medication treatment, and clinical outcome. Finally, despite the relatively large size for the trial itself, the sample size is still modest for a simulation analysis, which explains the large confidence intervals for the estimated predictive performances. A larger trial may also provide sufficient data to constrain more complex, nonlinear models and further improve predictive performance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Estimated probability of achieving prolonged abstinence. Box plot of estimated probability of prolonged abstinence with 10-fold cross validation, as a function of baseline ADHD severity rating score. As illustrated, when patients have a low-modest baseline ADHD severity, placebos appear superior to OROS-MPH. This effect is reversed at high baseline ADHD severity. The point of treatment efficacy equivalence is at ADHD-RS = 35. ADHD-RS, baseline ADHD severity rating score; OROS-MPH, osmotic-release methylphenidate.

FIGURE 2.

Estimating the improvement of clinical outcome with stratification of baseline severity (a) schematic for a clinical trial simulation analysis for comparing the effectiveness of a patient stratification decision as an intervention to improve outcome. (b) Results of the analysis show that if the “correct” medication were given, there is a significant improvement of overall rate of sustained abstinence (asterisks showing $p < 1E-3$, with Bonferroni correction). ADHD-RS, baseline ADHD severity rating score; NS, not significant.

FIGURE 3.

Performances of predictive models for prolonged smoke cessation (a) ROC Curves for comparing the predictive performances for cross-validated predictions for three different types of models, showing a modest predictive performance for individual treatment response. Models that do not incorporate the interaction term (in black solid line) do not perform better than chance. (b) Quantification of predictive performance comparing the three types of models, showing a modest, but statistically significant performance improvement with a model incorporating many covariates baseline covariates using L1-regularization, but only the small number of patients that the model is most confident about ($p < 1E-3$, with Bonferroni correction). ROC, Receiver Operating Characteristics; ADHD-RS, baseline ADHD severity rating score.

TABLE 1

Performance of predictive models for prolonged abstinence

MODEL FORM	ROC-AUC for prolonged abstinence	95% Confidence intervals (+/-)	<i>p</i> -Value
TREATMENT + ADHD-RS	.43	.12	.10
TREATMENT + ADHD-RS + TREATMENT * ADHD-RS	.59	.10	.09
TREATMENT + ADHD-RS + TREATMENT * ADHD-RS + AGE	.58	.12	.10
TREATMENT + ADHD-RS + TREATMENT * ADHD-RS + RACE	.58	.10	.08
TREATMENT + ADHD-RS + TREATMENT * ADHD-RS + MALE	.57	.08	.08
TREATMENT + ADHD-RS + TREATMENT * ADHD-RS + CRAVING	.58	.11	.09
TREATMENT + ADHD-RS + TREATMENT * ADHD-RS + WST	.57	.11	.08
TREATMENT + ADHD-RS + TREATMENT * ADHD-RS + FAGERSTROM	.59	.10	.10
TREATMENT + ADHD-RS + TREATMENT * ADHD-RS + EDUCATION (YRS)	.59	.11	.09
TREATMENT + ADHD-RS + TREATMENT * ADHD-RS + MARITAL STATUS	.59	.11	.08
TREATMENT + ADHD-RS + TREATMENT * ADHD-RS + LIFETIME DEPRESSION	.57	.08	.11
TREATMENT + ADHD-RS + TREATMENT * ADHD-RS + BASELINE BDI	.59	.09	.11
TREATMENT + ADHD-RS + TREATMENT* ADHD-RS + SITE (3 TYPES)	.58	.11	.10
ALL 2nd order Interactions (L1-regularized regression)	.53	.12	.10
ALL 2nd order interactions (L1-regularized regression) in only the most confident cases	.65	.11	.11

Predictive performance of the model with the addition of only the ADHD-RS * TREATMENT term yields the best predictive performance, and adding other baseline covariates as predictors does not improve predictive performance. *p*-Value for testing that the performance is significantly better than chance.

Abbreviations: ADHD-RS: baseline ADHD rating scale; WST: baseline nicotine withdrawal symptom score; ROC-AUC: Receiver-Operating Characteristics-Area Under the Curve; BDI - Beck Depression Inventory.