Published in final edited form as:

Drug Alcohol Depend. 2017 October 01; 179: 18–24. doi:10.1016/j.drugalcdep.2017.06.020.

ADHD symptoms impact smoking outcomes and withdrawal in response to Varenicline treatment for smoking cessation*

L. Cinnamon Bidwell¹, Hollis C. Karoly², Kent. E. Hutchison^{1,2}, and Angela D. Bryan^{1,2}

¹Institute of Cognitive Science, University of Colorado Boulder, UCB 344, Boulder, CO 80309-0345, USA

²Department of Psychology and Neuroscience, University of Colorado Boulder, UCB 344, Boulder, CO 80309-0345, USA

Abstract

Introduction—Attention-Deficit/Hyperactivity Disorder (ADHD) is associated with nicotine dependence and difficulty quitting smoking. Few cessation trials specifically consider the impact of ADHD on treatment outcomes, including those testing established pharmacological therapies, such as varenicline.

Methods—The current study focused on the impact of pretreatment ADHD inattention (IN) and hyperactivity-impulsivity (HI) symptoms on treatment outcome in a randomized controlled trial of varenicline [N=205, average age=34.13(10.07), average baseline cigarettes per day=14.71(7.06)]. Given that varenicline's putative therapeutic mechanism is attenuation of withdrawal severity during abstinence, we also tested changes in withdrawal as a mediator of treatment effects in high and low ADHD groups.

Results—ADHD symptom severity in this sample was in the subclinical range. Cessation was associated with HI, but not IN, such that high HI individuals on varenicline reported the lowest smoking levels at the end of treatment across all groups (3.06 cig/day for high HI vs 4.02 cig/day for low HI). Individuals with high HI who received placebo had the highest smoking at the end of

Correspondence: L. Cinnamon Bidwell, Institute of Cognitive Science, University of Colorado Boulder, 344 UCB, Boulder, CO 80309-0345, USA., Tel: 781-608-3711, lcb@colorado.edu.

Angela D. Bryan, angela.bryan@colorado.edu, Department of Psychology and Neuroscience, University of Colorado Boulder, UCB 344, Boulder, CO 80309-0345, USA, Tel: 303-492-9147, Fax: 303-492-2967

Hollis C. Karoly, hollis.karoly@colorado.edu, Department of Psychology and Neuroscience, University of Colorado Boulder, UCB 344, Boulder, CO 80309-0345, USA, Tel: 720-507-4317, Fax: 303-492-2967

Kent E. Hutchison, kent.hutchison@colorado.edu, Department of Psychology and Neuroscience, University of Colorado Boulder, UCB 344, Boulder, CO 80309-0345, USA, Tel: 303-492-9147, Fax: 303-492-2967

Author Disclosures

Contributions

Each author contributed directly to the design and preparation of the paper. ADB and KEH led the conceptualization and design of the larger clinical trial. LCB conceptualized the current study and led the analyses and write up. HCK supported the analysis and took the lead on writing key sections of the manuscript. ADB was the senior statistician and provided guidance on the statistical modeling and mediation analyses. All authors reviewed the final version of the manuscript.

Conflict of interest

There are no conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

treatment (7.69 cigs/day for high HI vs 5.56 cig/day for low HI). Patterns continued at follow-up. Varenicline significantly reduced withdrawal for those with high HI, but not low HI. However, path models did not support an indirect effect of medication on reducing smoking via withdrawal in either group, suggesting that unmeasured variables are involved in varenicline's effect on reducing smoking.

Conclusions—These data add to a gap in the smoking cessation literature regarding the impact of ADHD symptoms on the efficacy and mechanisms of frontline pharmacological treatments.

Keywords

withdrawal; quitting smoking; impulsivity; nicotine; inattention

1.0 Introduction

While a large proportion of smokers are motivated to quit smoking and a number of available treatments improve quit rates, relapse is still common, with only 10–40% achieving long-term abstinence even after undergoing intensive treatment (USDHHS, 2008). While the literature has been instrumental in providing guidelines for statistical analysis and measurement of outcomes and mediators in smoking cessation clinical trials (Hall et al., 2001; Hughes et al., 2003), less attention has been paid to patient characteristics that may clinically impact cessation-related processes. Specifically, smoking cessation has not been systematically examined in the context of many psychiatric disorders, with some notable exceptions being schizophrenia and anxiety/depression, which have received recent attention with regard to their impact on smoking outcomes (Leventhal et al., 2008; Tidey et al., 2005). However, Attention Deficit/Hyperactivity Disorder (ADHD) is strongly associated with nicotine dependence (ND; McClernon and Kollins, 2008) and heightens risk for persistent smoking and poorer cessation (Humfleet et al., 2005; Rukstalis et al., 2005). Although several theoretical mechanisms have been proposed for this overlap, including altered drug reward and withdrawal processes related to ADHD and the neurobiological overlap among ADHD and the action of nicotine, the mechanism underlying this association have not been systemically examined (Kollins et al., 2013; McClernon and Kollins, 2008). Further, despite its importance, ADHD is rarely assessed or targeted in smoking treatment trials, an issue highlighted in several recent reviews (Bidwell and Leventhal, 2013; Gray and Upadhyaya, 2009).

Adult ADHD is classified by the presentation of five or more symptoms of inattention (IN) and/or five or more symptoms of hyperactivity/impulsivity (HI) to a degree that causes clinically significant impairment in two or more areas of the individual's life (A.P.A., 2013). While primarily defined as a disorder that onsets in childhood, ADHD symptoms persist into adulthood, with recent meta-analyses estimating the population prevalence of clinical ADHD is similar in children (5.7%) and adults (5.0%; Polanczyk et al., 2007; Polanczyk et al., 2014). Given the strong evidence that ADHD exists on the extreme end of a continuum of attentional processes and hyperactive/impulsive behavior (Levy et al., 1997), researchers have advocated for analyzing continuous measures of ADHD rather than categorical diagnoses (Willcutt et al., 2012). Prior research in non-clinical smoking samples suggests a linear relationship between increasing levels of current ADHD symptoms and important

smoking outcomes in adults, suggesting that gradations of ADHD symptoms that do not meet diagnostic criteria associate with variation in processes that are clinically relevant to cessation and relapse (Ameringer and Leventhal, 2013). Further, there is strong evidence that the IN and HI symptom dimensions of ADHD fall into empirically distinguishable factors with distinct functional and neuropsychological impairment profiles (Willcutt et al., 2012). There may also be differential impacts of IN and HI on smoking outcomes (Covey et al., 2011; Fuemmeler et al., 2007), with some studies suggesting that IN symptoms drive this association (Tercyak et al., 2002), and others suggesting that HI symptoms are more predictive of smoking (Elkins et al., 2007; Fuemmeler et al., 2007). Thus, in order to meaningfully contribute to the understanding of poorer clinical outcomes in individuals with ADHD, studies should measure ADHD linearly and distinguish between the two ADHD symptom dimensions.

Lower abstinence rates have been observed among smokers with predominantly HI than those with predominantly IN symptoms (Covey et al., 2008). Further, recent laboratory work demonstrated that smokers with higher levels of ADHD symptoms, particularly HI symptoms, were more likely to endorse withdrawal symptoms (e.g., negative affect, concentration problems, and desire to smoke) during periods of controlled abstinence (Bidwell et al., 2014). Thus, ADHD symptoms even below diagnostic thresholds, particularly HI, are associated with more severe exacerbations in abstinence-induced withdrawal, which could contribute directly to poorer ADHD quit rates. Preliminary clinical data suggest higher levels of withdrawal, negative affect, and craving are present in ADHD smokers making a cessation attempt (McClernon et al., 2011). These abstinence-induced changes could be interpreted as an unmasking or exacerbation of ADHD symptoms caused by smoking discontinuation, or as a more pronounced effect of nicotine withdrawal. Regardless of the interpretation, data across multiple methods suggest that smokers with ADHD symptoms are likely to be more motivated to resume smoking following abstinence to suppress withdrawal symptoms.

Despite studies showing that smokers with ADHD report more failed quit attempts, lower rates of cessation, and more severe withdrawal than their non-diagnosed counterparts (Humfleet et al., 2005), the impact of ADHD on treatment outcome has not been well-examined for smoking cessation pharmacotherapies. Regarding smoking cessation, varenicline is a first-line treatment, with some head-to-head studies suggesting that varenicline may be more effective than other first line medications such as nicotine replacement and bupropion (Aubin et al., 2008; Gonzales et al., 2006; Nides et al., 2006) and others suggesting it is similarly effective to nicotine replacement therapies (Baker et al., 2016). Preclinical studies indicate that varenicline acts as a partial agonist at the $\alpha 4\beta 2$ nicotinic acetylcholine receptor (nAChR), with both agonist and antagonist effects (Coe et al., 2005; Rollema et al., 2007). Varenicline is thought to reduce craving and attenuate withdrawal, restlessness, and negative affect during abstinence, potentially via its antagonist action at $\alpha 4\beta 2$ nAChRs, which play a role in mediating nicotine reinforcement (Aubin et al., 2008; Stapleton et al., 2008). Thus, varenicline may be uniquely efficacious for particular smokers, namely those with high levels of ADHD symptoms, who find it hard to cope with withdrawal during quit attempts.

1.1 Purpose of the Current Study

Although data suggest more severe withdrawal and difficulty quitting in individuals with ADHD, little is known about how to best approach treating smokers with high levels of ADHD symptoms to optimize clinical outcomes. Thus, the current study focused on the impact of pretreatment ADHD symptoms on treatment outcome in a randomized controlled trial (RCT) of varenicline in a community sample of smokers. Although the sample is not a selected for clinical ADHD, subthreshold ADHD symptoms are likely to be present at higher rates in smokers (Kollins et al., 2005), suggesting that examining the impact of subclinical ADHD variation on smoking outcomes in the context of cessation would provide informative data on individual differences that impact treatment processes. Given established data on differential roles for IN and HI in relation to smoking outcomes, we examined the extent to which gradations in IN and HI symptoms impacted treatment outcomes across medication and placebo conditions. Further, in light of data suggesting that 1) the putative mechanism for the efficacy of varenicline in cessation is its effect on attenuation of withdrawal symptoms during quit attempts and 2) individuals with higher levels of ADHD symptoms experience greater severity of withdrawal during smoking abstinence, we tested a cross groups mediational model in which changes in withdrawal served as a mediator of treatment effects in individuals with high versus low ADHD symptoms. In addition, we tested a moderated mediational model examining whether changes in withdrawal differentially mediated the effects of varenicline on smoking outcomes for individuals with high vs. low ADHD symptoms. Primary cessation outcomes are reported in a separate paper and support the effectiveness of varenicline over placebo (Littlewood et al., 2017).

2.0 Method

The study was approved by the local ethics committee, written informed consent was obtained, and the study was registered at ClinicalTrials.gov (identifier: NCT01228175).

2.1 Participants

Individuals between the ages of 18 and 55 were recruited for a “Quit Smoking” study via radio, newspaper, flyers, and Craigslist in a mid-size southwestern city between 11/09 and 9/14. Interested individuals were asked screening questions via phone. Individuals who indicated that they a) smoke at least 10 cigarettes/day, b) have not previously taken varenicline, c) have had no serious medical or psychiatric condition in the past 6 months, d) are not currently pregnant or nursing were scheduled for an in-person screening. This included assessments of substance use and psychological history as well as a physical with the study physician. Participants were excluded for the following reasons: a) self-reported or physician-identified health concerns; b) currently taking insulin or oral hypoglycemic medication; c) self-reported use of illicit drugs (excluding marijuana) in the previous 60 days or a positive urine toxicology screen for use of cocaine, methamphetamine, heroin, or other illicit drugs; d) met Diagnostic and Statistical Manual of Mental Disorders, version IV (*DSM-IV*) criteria for psychotic disorder, bipolar disorder or major depression in the past year (27 individuals reported a history of having a had at least one major depressive episode prior to one year before they enrolled into the study).

2.2 Procedure and Sample Size

Clinical Trial Design—All study procedures are described in detail in Littlewood et. al., 2017 according to CONSORT guidelines. The present study followed a double-blind, placebo-controlled design. Eligible subjects were randomly assigned to receive varenicline or placebo for 12 weeks, resulting in 111 individuals randomized to Varenicline and 94 to placebo. Assessments were obtained at a baseline session prior to the quit date, as well as at 2, 6, and 12 weeks (the end of treatment) later. A follow-up assessment was collected 6 months post-treatment. All subjects received a baseline motivational enhancement and met briefly with their assigned therapist at each assessment during the treatment phase. Consistent with previous trials (Gonzales et al., 2006), patients were titrated as follows: days 1–3, 0.5 mg/day; days 4–7, 0.5 mg 2x/day, and after day 7, 1 mg 2x/day. Detailed information about interventions, medication administration, and adherence procedures are provided in Supplementary Information¹.

2.3 Measures

In order to leverage the power improvement by using a continuous outcome measure as well as to be consistent with the primary outcome study, average cigarettes per day at each time point was used as the smoking outcome assessment (Littlewood et al., 2017). Participants' demographic characteristics (i.e., age, sex, ethnicity, employment, income, and education), smoking history (i.e., frequency and quantity of tobacco use, past quit attempts) were assessed at baseline. In addition, for screening purposes, the Structured Clinical Interview for DSM-IV, Research Version (SCID) was used to assess current and lifetime psychological disorders. In order to control for baseline levels of nicotine dependence (ND) and negative affect in the models assessing the impact of ADHD, ND was characterized using the Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991), depression/negative affect was assessed using the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), and anxiety was assessed using the Beck Anxiety Inventory (BAI; Beck and Steer, 1990).

ADHD symptoms—ADHD Symptom Checklist (Barkley and Murphy, 1998) is a DSM based 18-item self-report screening scale for ADHD symptoms over the prior six months. The items are on a scale from 0–3 (0=never; 1=sometimes; 2=often; 3=very often). The primary models in the current study examined severity scores derived from the two subscales each comprised of the sum of nine items, that assess the frequency of IN (e.g., “How often do you make careless mistakes when you have to work on a boring or difficult project?”) and HI (e.g., How often do you fidget or squirm with your hands or your feet when you have to sit down for a long time?”). In secondary models that considered symptom counts, a rating of 1 or higher was considered endorsement of that symptom. Self-report rating scales are a reliable and valid approach to characterizing adult ADHD symptoms and may be more generalizable than an ADHD diagnosis to the broader population of smokers (Kollins et al., 2005).

¹Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

2.4 Overview of Analyses and Power

All measures were examined for distributional properties. Treatment groups were compared on demographic variables via T-tests (continuous variables) and chi-square tests (categorical variables) to test the effectiveness of random assignment. The interrelationships among the ADHD subscales and withdrawal measures were calculated.

A priori power analyses suggested that, by conservatively predicting a small to moderate interaction effect among condition and ADHD symptoms (assuming a $d = .35$), we would require a total $n = 204$ divided across treatment groups. Since the moderator analyses were planned *a priori* (Shadish et al., 2002), and because of the difficulty in detecting interactions in field studies (McClelland and Judd, 1993), critical alpha was maintained at .05 for the primary analyses. Missing data were approached with an intent-to-treat strategy via the use of full information maximum likelihood (FIML) estimation, whereby all possible data points are utilized and missing values are iteratively estimated using the expectation-maximization algorithm (Little and Rubin, 2014; Schafer and Graham, 2002). Moderator analyses of outcomes were conducted in a random coefficient regression (RCR; Cohen et al., 2013) framework via SAS Proc Genmod, which takes into account the non-normal distribution of our primary outcome (Average cigarettes per day across treatment) and the longitudinal nature of the data and implements FIML estimation of missing data (Schafer and Graham, 2002). Average cigarettes/day reported at baseline, 2 week, 6 week, 12 week (end of treatment phase), 36 week (follow-up) sessions served as the dependent measure, and condition (varenicline vs. placebo) and time were the independent variables. ADHD IN and HI subscales served as the moderator variables in two separate moderation models. For each ADHD subscale (IN and HI), we estimated a RCR wherein condition, time, the moderator, and all possible interactions served as the independent variables. Drug condition was coded 0=placebo, 1=varenicline. The test of primary interest in these analyses is the time X condition X ADHD moderator interaction. In order to test for effects of ADHD over and above baseline differences in ND and comorbid negative effect, we chose *a priori* covariates that were directly relevant to our analysis involving ADHD; specifically baseline FTND and BDI-II were included, along with age and sex, as covariates in all models. In the parent study (Littlewood et al., 2017), impulsivity and personality style emerged as moderators of the relationship between medication condition and treatment outcome. While the personality variables (openness and agreeableness as measured by the Neuroticism, Extraversion, Openness Five-Factor Inventory (NEO-FFI; Costa and McCrae, 1997) showed some small and interesting effects, we viewed these traits as less directly relevant to a clinical disorder such as ADHD and thus did not include them. Impulsivity (as measured by the Barratt Impulsivity Scale (BIS-11; Patton et al., 1995) required more careful consideration. There is both conceptual and statistical ($r = .37$) overlap between the BIS and ADHD-HI symptoms. Given that we were testing a three-way interaction (a small effect under the best of circumstances; (McClelland and Judd, 1993) multicollinearity of even that relatively small magnitude is problematic. Thus, we determined that we did not have the power to include both in the model.

In addition, based on data demonstrating more severe withdrawal profiles in individuals with high levels of ADHD symptoms and, further, data suggesting that the efficacy of varenicline

is due to its role in attenuating withdrawal symptoms during smoking abstinence, where a significant time X condition X ADHD interaction was found, we tested a moderated mediational model in order to examine whether changes in withdrawal differentially mediated the effects of varenicline on smoking outcomes for individuals with high vs. low symptoms on the particular ADHD subscale.

3.0 Results

3.1 Demographics, ADHD, and Smoking Outcomes

Participant characteristics and mean scores on smoking variables and ADHD symptom severity for the HI and IN subscales are provided in Table 1. No smoking or demographic variables differed between groups. Correlations among ADHD subscales, baseline smoking characteristics, and measures of anxiety and depressive symptom severity are presented in Supplemental Table S1².

3.1.1 ADHD—The ADHD scales exhibited good internal reliability: IN, $\alpha=.82$, HI, $\alpha=.76$, overall scale $\alpha=.87$. As expected, IN and HI subscales were significantly correlated ($r=.66$, $p<.001$). Average ADHD symptoms across the sample was within the subclinical range (HI mean=4.23, $SD=3.38$; IN mean=3.47, $SD=3.36$, ADHD total mean=7.76 $SD=6.17$).

3.1.2 ADHD as a Moderator of Treatment Outcome—Standardized estimates for main effects and interactions are reported in Table 2. IN did not moderate the effect of treatment (Varenicline vs placebo) over time. However, there was a significant time X treatment X HI interaction, suggesting that baseline HI symptoms did moderate the effect of treatment condition over time ($\beta=-0.04$, S.E.=0.02, $p=0.02$). This moderating effect of HI was present over and above baseline levels of ND, negative mood (BDI-II), age, and sex.

Although ADHD symptoms were treated continuously in the primary analyses, in Figure 1 we provide the unadjusted means for average cigarettes smoked/day across the five assessment time points (Baseline through Week 36) in the two treatment conditions in groups of individuals with both high (≥ 5 symptoms; $n=77$) and low HI (<5 symptoms, $n=128$) as defined by DSM-5 symptom cut offs. Despite higher levels of ADHD being associated with treatment outcomes, the current study suggests that varenicline reduced cigarettes/day in high and low ADHD groups, and is potentially more effective in the high HI group. In the varenicline group, lower HI was associated with smoking 4.02 cig/day at the end of treatment (week 12) and higher HI individuals reported smoking 3.06 cig/day at week 12. At follow-up, the groups reported similar smoking levels, with high HI individuals in the varenicline group smoking 4.8 cigs/day at Week 36, whereas those with lower HI reported smoking 4.97 cigs/day. Thus, in addition to reduced smoking during the course of varenicline treatment, high HI and low HI individuals were both successful at maintaining reductions once off the medication compared to those with lower HI. In the placebo condition, high HI individuals had the poorest outcomes, reporting 7.69 cigs/day at the end of treatment, whereas low HI individuals smoked 5.56 cigs/day. At follow-up, high HI

²Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

individuals who received placebo continued to have the poorest outcomes, smoking the most cigarettes (9.19 cigs/day) across any of the groups, time points, and treatment conditions.

3.1.3 Cross-groups (High vs. Low HI) Moderated Mediation of Medication

Condition on Smoking Outcomes via Changes in Withdrawal—Based on data suggesting that varenicline is effective at reducing smoking via its role in attenuating withdrawal during abstinence and data suggesting that individuals with high levels of ADHD experience greater withdrawal during abstinence, we followed up our primary moderation model with a moderated mediation model that examined whether changes in withdrawal differentially mediated the effects of varenicline on smoking outcomes for individuals with high versus low HI symptoms. Initial correlations suggested a significant relationship among HI symptoms and baseline withdrawal severity ($r=.310$, $p<.001$). For the cross-groups mediation model, the high ($n=77$) and low HI ($n=128$) groups were defined identical to those reported above and in Figure 1 (≥ 5 =high HI and <5 =low HI), again consistent with DSM-5 adult ADHD.

A cross-groups path model (Aiken et al., 1994; Bentler; Bryan et al., 2005) was then estimated in EQS v6.2 (Bentler), such that the exact model in Figure 2 was estimated simultaneously in low versus high HI symptom groups. As illustrated in Figure 2, medication condition was the sole exogenous variable, and the mediator was the change in withdrawal from baseline to end of treatment (Week 12). The outcome variable was smoking at the end of treatment (Week 12). First, a model was estimated where all three structural paths were constrained to equality in the two groups. The fit of this model was not adequate, χ^2 (3, $n=205$)=8.61, $p<.05$, CFI=.62, and Lagrange multiplier statistics (MacCallum, 1995), suggested that freeing two parameters upon which the two groups significantly differed would improve the fit of the model. The parameters from medication condition to changes in withdrawal, and from changes in withdrawal to smoking outcomes were thus freely estimated in a second model. A two degree of freedom χ^2 test of change in fit (χ^2 , (Hayduk, 1987) was conducted. A significant change in χ^2 indicates that the paths tested are significantly different in the two groups, i.e., that the mediated effect is moderated by group. In this case, the change in χ^2 was significant, χ^2 (2, $n=205$)=6.65, $p<.05$. In addition, the overall model fit with these paths freed improved and was acceptable, χ^2 (1, $n=205$)=1.967, $p=.16$, CFI=.93.

The path from medication to changes in withdrawal was nonsignificant for those with low HI ($\beta=.11$), but was positive and significant for those with high HI ($\beta=.32$, $p<.05$). However, changes in withdrawal differentially affected smoking outcomes. For those with low HI larger changes in withdrawal were associated with less smoking at week 12 ($\beta=-.27$, $p<.05$), while for those with high HI changes in withdrawal were not associated with smoking outcomes ($\beta=-.03$). For both groups, it was clear that mediation of medication effects on smoking outcomes via withdrawal was incomplete and results supported a significant relationship between medication condition and smoking outcomes that was not mediated by changes in withdrawal.

4.0 Discussion

Findings suggest that gradations in ADHD HI symptoms impacted treatment outcomes in several ways. First, both high and low HI individuals were successful on varenicline during the treatment phase and this success extended into the follow-up period. Second, high HI individuals in the placebo group had the poorest smoking outcomes across treatment groups, suggesting that these individuals are at-risk for cessation failure, and are not likely to benefit from ineffective or placebo treatments. Further, mediation models supported a differential impact of varenicline on reducing withdrawal symptoms in high HI individuals. However, the indirect pathway from medication to smoking reductions via withdrawal attenuation was not fully supported in either group. Thus, our findings of poor outcomes under the placebo condition support the notion that smokers with ADHD symptoms do poorly during cessation efforts (Covey et al., 2008; Sullivan and Rudnik-Levin, 2001) and those of successful findings in the varenicline condition suggest that pharmacological efforts may improve outcomes in this hard-to-treat group.

The finding that the HI symptom index is a more consistent predictor of treatment outcome effects than IN is consistent with prior epidemiological work showing that while both IN and HI were associated with ND, HI was associated with poorer cessation outcomes (Kollins et al., 2005). In addition, data that high HI individuals and those lower levels of HI symptoms were successful in the varenicline condition, a medication which is thought to pharmacologically target withdrawal symptoms, are consistent with studies suggesting that gradations in HI are associated with greater withdrawal severity, including craving and negative affect, during smoking abstinence in laboratory controlled and clinical settings (Bidwell et al., 2014; Covey et al., 2008). In addition, that high HI individuals reported greater smoking in the placebo group suggests that in a treatment context, these individuals may be particularly susceptible to smoking reinstatement when cessation and abstinence affects are not pharmacologically or otherwise managed. These findings provide preliminary support for the efficacy of varenicline in those with higher levels of ADHD symptoms and underscore the importance of considering ADHD in smoking treatment.

Tests of withdrawal attenuation as a mediator of treatment effects in individuals with high and low HI symptoms suggested a partial confirmation of our hypothesis that varenicline may be relevant to smokers with ADHD due to its putative impact on attenuation of withdrawal. As noted in Figure 2, our mediational findings indicate that varenicline impacts withdrawal for the high HI group but not the low HI group. This suggests that varenicline differentially and more strongly impacted withdrawal severity in the high HI group. These data are relevant clinically as individuals with ADHD report greater withdrawal severity and discomfort during abstinence, which has been linked to poor quit rates in this population. Whether HI in this context more strictly reflects subthreshold ADHD symptoms or taps a more general latent impulsivity construct is unclear. However, these findings are also partially consistent with studies linking impulsivity and smoking abstinence (Harrison et al., 2009) and those suggesting that smokers with impulsive traits tend to smoke for withdrawal relief (Doran et al., 2009). However, our model did not support the idea that change in withdrawal was significantly associated with smoking reductions for the high HI group. Thus, although varenicline appears to directly impact withdrawal in the high HI group, the

mediation model is not fully consistent with an indirect effect of the medication on reducing smoking through withdrawal in high HI individuals. Further, because the direct path from medication to smoking outcome remains significant when withdrawal change is included as a mediator, it is likely that additional mechanistic variables not included in the current mediation model are involved in varenicline's smoking reduction effects in both groups.

One explanation for these findings in the high HI group may be that, in addition to attenuating withdrawal symptoms, varenicline reduces ADHD symptoms. Given that dysfunction within dopaminergic systems is implicated in the pathophysiology of ADHD (Volkow et al., 2009), varenicline's impact on striatal dopamine transmission (Di Ciano et al., 2016; Feduccia et al., 2014) may serve to reduce the severity of ADHD symptoms via facilitation of dopamine transmission within brain regions associated with reward and motivation, such as the striatum. These molecular actions may also explain varenicline's efficacy in reducing withdrawal, given that nicotine withdrawal is associated with reductions in basal dopamine levels in the striatum (Zhang et al., 2012). Overall, because nicotine has been linked to reduction of ADHD symptoms (Conners et al., 1996; Potter et al., 2014), it is possible that varenicline may contribute to successful decreases smoking in individuals with high HI, partially through an effect on reducing ADHD symptoms in concert with changing smoking behavior. Future research examining ADHD symptom dimensions over the course of varenicline treatment is necessary to shed light on this hypothesis.

4.1 Limitations

ADHD symptoms were assessed via self-report and only at baseline, thus we could not track changes in symptoms over time. Also, we focused on a community sample, rather than a sample specifically recruited for ADHD, and thus did not assess treatment effects in individuals with clinical ADHD. This is a strength and weakness of the design in that we cannot speak directly to the effects of varenicline in those with an ADHD diagnosis. However, our results suggesting that subclinical gradations in HI symptoms are relevant to cessation processes may generalize to a broader population of smokers who tend to present with elevated ADHD symptoms, which may not meet full diagnostic criteria. Relatedly, the subclinical nature of ADHD is somewhat diffuse, and, as would be expected, measures of affective symptom severity were moderately correlated with ADHD symptoms (See Supplemental Table S1³). Further, not all common comorbidities (e.g., sleep difficulties, clinical anxiety disorders) were assessed or excluded in the present study, which may impact generalizability of these findings. Moreover, we had only one participant in each condition report taking ADHD medication during the study, so we can say little about the combined effects of varenicline and stimulant medication on smoking cessation. This is an important future direction, as a recent case report suggests that the smoking cessation effects of varenicline may be interrupted by the psycho-stimulant amphetamine-dextroamphetamine (Whitley and Moorman, 2007). The trial was not originally designed to test the moderating effect of ADHD on treatment outcomes, and thus we did not have the statistical power to include the full suite of potentially important covariates including, critically, the BIS. Related, the significant medication X time interaction reported in the parent trial (Littlewood

³Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

et al., 2017) was superseded in our analysis by the three-way interaction with ADHD symptomatology. Both of these findings suggest that a well-designed and fully powered trial that selectively focuses on ADHD symptomatology at the outset would be a critical next step for research. Finally, although our study did not have a measure targeting the rewarding aspects of smoking across treatment, alterations of drug reward is another pathway thought to explain the efficacy of varenicline that may also overlap with the neurobiology of ADHD smokers (Kollins et al., 2013) and should be considered in future work.

Despite these limitations, our findings reflect associations of self-reported HI symptoms to treatment outcome, suggesting that HI may be an important marker of the ADHD syndrome that is relevant to treatment. Therefore, researchers and clinicians focused on smoking treatment should measure ADHD at the symptom dimension level. In addition, our results extend to individuals who may not cross the threshold for ADHD diagnosis. Although large numbers of smokers in our sample reported elevations in ADHD symptoms (e.g., 77 endorsed ≥ 5 HI symptoms at some level), only 2% of our sample self-reported clinically-significant ADHD concordant with an ADHD diagnosis. Thus, relying solely on categorical diagnostic thresholds may overlook subclinical variation across the ADHD continuum that could be important to cessation. Given that subthreshold ADHD symptoms are likely to be present at higher rates in smokers, our findings potentially generalize more broadly to smokers beyond those with an ADHD diagnosis.

5.0 Conclusions

This study adds to the dearth of research addressing ADHD in smoking cessation trials. Results are promising in that varenicline was efficacious in reducing smoking in individuals with higher levels of ADHD symptoms, a group that traditionally report more difficulty quitting and higher rates of withdrawal during abstinence (McClernon et al., 2011). These findings are consistent with the notion that ADHD plays a complex role in cessation outcomes related to varenicline (Gray and Upadhyaya, 2009; Whitley and Moorman, 2007) and promote the consideration of ADHD in smoking cessation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Role of Funding Source

This research is supported by the National Institute on Drug Abuse: R01DA025074 to KEH and K23DA033302 to LCB. HCK is supported by National Science Foundation Graduate Research Fellowship Program, Grant DGE 1144083.

References

A.P.A. Diagnostic and Statistical Manual of Mental Disorders. 5. American Psychiatric Association; Washington D.C: 2013. DSM-V

- Aiken LS, Stein JA, Bentler PM. Structural equation analyses of clinical subpopulation differences and comparative treatment outcomes: Characterizing the daily lives of drug addicts. *J Consult Clin Psychol.* 1994; 62:488–499. [PubMed: 8063975]
- Ameringer KJ, Leventhal AM. Associations between Attention Deficit Hyperactivity Disorder Symptom Domains and DSM-IV Lifetime Substance Dependence. *Am J Addict.* 2013; 22:23–32. [PubMed: 23398223]
- Aubin HJ, Bobak A, Britton JR, Oncken C, Billing CB Jr, Gong J, Williams KE, Reeves KR. Varenicline versus transdermal nicotine patch for smoking cessation: Results from a randomised open-label trial. *Thorax.* 2008; 63:717–724. [PubMed: 18263663]
- Baker TB, Piper ME, Stein JH, Smith SS, Bolt DM, Fraser DL, Fiore MC. Effects of nicotine patch vs Varenicline vs combination nicotine replacement therapy on smoking cessation at 26 weeks: A randomized clinical trial. *JAMA.* 2016; 315:371–379. [PubMed: 26813210]
- Barkley, R., Murphy, KR. Attention-deficit Hyperactivity Disorder: A Clinical Workbook. 2. Guilford Press; 1998.
- Beck, A., Steer, R., Brown, G. Manual for the BDI-II. Psychological Corporation; San Antonio, TX: 1996.
- Beck, AT., Steer, RA. Manual for the Beck anxiety inventory. 1990.
- Bentler, P. EQS 6 Structural Equations Program Manual. Multivariate Software. Inc Google Scholar; Encino, CA: 2006.
- Bidwell LC, Ameringer KJ, Leventhal AM. Associations of attention-deficit hyperactivity disorder symptom dimensions with smoking deprivation effects in adult smokers. *Psychol Addict Behav.* 2014; 28:182–192. [PubMed: 24731115]
- Bidwell LC, Leventhal AM. The importance of considering ADHD in smoking cessation clinical trials. *Clin Invest.* 2013; 3:511–514.
- Bryan A, Rocheleau CA, Robbins RN, Hutchinson KE. Condom use among high-risk adolescents: Testing the influence of alcohol use on the relationship of cognitive correlates of behavior. *Health Psychol.* 2005; 24:133–142. [PubMed: 15755227]
- Coe JW, Brooks PR, Wirtz MC, Bashore CG, Bianco KE, Vetelino MG, Arnold EP, Lebel LA, Fox CB, Tingley FD 3rd, Schulz DW, Davis TI, Sands SB, Mansbach RS, Rollema H, O'Neill BT. 3,5-Bicyclic aryl piperidines: A novel class of alpha4beta2 neuronal nicotinic receptor partial agonists for smoking cessation. *Bioorganic Med Chem Letter.* 2005; 15:4889–4897.
- Cohen, J., Cohen, P., West, SG., Aiken, LS. Applied multiple regression/correlation analysis for the behavioral sciences. Routledge; 2013.
- Conners CK, Levin ED, Sparrow E, Hinton SC, Erhardt D, Meck WH, Rose JE, March J. Nicotine and attention in adult attention deficit hyperactivity disorder (ADHD). *Psychopharmacol Bull.* 1996; 32:67–73. [PubMed: 8927677]
- Costa PT Jr, McCrae RR. Stability and change in personality assessment: The revised NEO Personality Inventory in the year 2000. *J Pers Assess.* 1997; 68:86–94. [PubMed: 9018844]
- Covey LS, Hu MC, Weissman J, Croghan I, Adler L, Winhusen T. Divergence by ADHD subtype in smoking cessation response to OROS-methylphenidate. *Nicotine Tob Res.* 2011; 13:1003–1008. [PubMed: 21652734]
- Covey LS, Manubay J, Jiang H, Nortick M, Palumbo D. Smoking cessation and inattention or hyperactivity/impulsivity: A post hoc analysis. *Nicotine Tob Res.* 2008; 10:1717–1725. [PubMed: 19023824]
- Di Ciano P, Guranda M, Lagzdins D, Tyndale RF, Gamaledin I, Selby P, Boileau I, Le Foll B. Varenicline-induced elevation of dopamine in smokers: A preliminary [(11)C]-(+)-PHNO PET Study. *Neuropsychopharmacology.* 2016; 41:1513–1520. [PubMed: 26442600]
- Doran N, Cook J, McChargue D, Spring B. Impulsivity and cigarette craving: Differences across subtypes. *Psychopharmacology.* 2009; 207:365–373. [PubMed: 19756522]
- Elkins IJ, McGue M, Iacono WG. Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder, and sex on adolescent substance use and abuse. *Arch Gen Psychiatry.* 2007; 64:1145–1152. [PubMed: 17909126]

- Feduccia AA, Simms JA, Mill D, Yi HY, Bartlett SE. Varenicline decreases ethanol intake and increases dopamine release via neuronal nicotinic acetylcholine receptors in the nucleus accumbens. *Br J Pharmacol*. 2014; 171:3420–3431. [PubMed: 24628360]
- Fuemmeler BF, Kollins SH, McClernon FJ. Attention deficit hyperactivity disorder symptoms predict nicotine dependence and progression to regular smoking from adolescence to young adulthood. *J Pediatr Psychol*. 2007; 32:1203–1213. [PubMed: 17602186]
- Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves KR. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: A randomized controlled trial. *JAMA*. 2006; 296:47–55. [PubMed: 16820546]
- Gray KM, Upadhyaya HP. Tobacco smoking in individuals with attention-deficit hyperactivity disorder: Epidemiology and pharmacological approaches to cessation. *CNS Drugs*. 2009; 23:661–668. [PubMed: 19594195]
- Hall SM, Delucchi KL, Velicer WF, Kahler CW, Ranger-Moore J, Hedeker D, Tsoh JY, Niaura R. Statistical analysis of randomized trials in tobacco treatment: Longitudinal designs with dichotomous outcome. *Nicotine Tob Res*. 2001; 3:193–202. [PubMed: 11506764]
- Harrison EL, Coppola S, McKee SA. Nicotine deprivation and trait impulsivity affect smokers' performance on cognitive tasks of inhibition and attention. *Exp Clin Psychopharmacol*. 2009; 17:91–98. [PubMed: 19331485]
- Hayduk, LA. Structural equation modeling with LISREL: Essentials and advances. JHU Press; 1987.
- Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: A revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict*. 1991; 86:1119–1127. [PubMed: 1932883]
- Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measures of abstinence in clinical trials: issues and recommendations. *Nicotine Tob Res*. 2003; 5:13–25. [PubMed: 12745503]
- Humfleet GL, Prochaska JJ, Mengis M, Cullen J, Munoz R, Reus V, Hall SM. Preliminary evidence of the association between the history of childhood attention-deficit/hyperactivity disorder and smoking treatment failure. *Nicotine Tob Res*. 2005; 7:453–460. [PubMed: 16085513]
- Kollins SH, English JS, Roley ME, O'Brien B, Blair J, Lane SD, McClernon FJ. Effects of smoking abstinence on smoking-reinforced responding, withdrawal, and cognition in adults with and without attention deficit hyperactivity disorder. *Psychopharmacology*. 2013; 227:19–30. [PubMed: 23247366]
- Kollins SH, McClernon FJ, Fuemmeler BF. Association between smoking and attention-deficit/hyperactivity disorder symptoms in a population-based sample of young adults. *Arch Gen Psychiatry*. 2005; 62:1142–1147. [PubMed: 16203959]
- Leventhal AM, Ramsey SE, Brown RA, LaChance HR, Kahler CW. Dimensions of depressive symptoms and smoking cessation. *Nicotine Tob Res*. 2008; 10:507–517. [PubMed: 18324570]
- Levy F, Hay DA, McStephen M, Wood C, Waldman I. Attention-deficit hyperactivity disorder: A category or a continuum? Genetic analysis of a large-scale twin study. *J Am Acad Child Adolesc Psychiatry*. 1997; 36:737–744. [PubMed: 9183127]
- Little, RJ., Rubin, DB. Statistical analysis with missing data. John Wiley and Sons; 2014.
- Littlewood R, Claus E, Wilcox C, Mickey J, Arenella P, Bryan A, Hutchinson KE. Moderators of smoking cessation outcomes in a randomized-controlled trial of Varenicline versus placebo. *Psychopharmacology*. 2017; 14:343–50.
- MacCallum, RC. Structural equation modeling: Concepts, issues, and applications. Sage Publications, Inc; Thousand Oaks, CA, US: 1995. Model specification: Procedures, strategies, and related issues; p. 16-36.
- McClelland GH, Judd CM. Statistical difficulties of detecting interactions and moderator effects. *Psychol Bull*. 1993; 114:376–390. [PubMed: 8416037]
- McClernon FJ, Kollins SH. ADHD and smoking: From genes to brain to behavior. *Ann NY Acad Sci*. 2008; 1141:131–147. [PubMed: 18991955]
- McClernon FJ, Van Voorhees EE, English J, Hallyburton M, Holdaway A, Kollins SH. Smoking withdrawal symptoms are more severe among smokers with ADHD and independent of ADHD

- symptom change: results from a 12-day contingency-managed abstinence trial. *Nicotine Tob Res.* 2011; 13:784–792. [PubMed: 21571687]
- Nides M, Oncken C, Gonzales D, Rennard S, Watsky EJ, Anziano R, Reeves KR. Smoking cessation with varenicline, a selective $\alpha 4 \beta 2$ nicotinic receptor partial agonist: Results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. *Arch Intern Med.* 2006; 166:1561–1568. [PubMed: 16908788]
- Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. *J Clin Psychol.* 1995; 51:768–774. [PubMed: 8778124]
- Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: A systematic review and meta-regression analysis. *Am J Psychiatry.* 2007; 164:942–948. [PubMed: 17541055]
- Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: An updated systematic review and meta-regression analysis. *Int J Epidemiol.* 2014; 43:434–442. [PubMed: 24464188]
- Potter AS, Schaubhut G, Shipman M. Targeting the nicotinic cholinergic system to treat attention-deficit/hyperactivity disorder: Rationale and progress to date. *CNS Drugs.* 2014; 28:1103–1113. [PubMed: 25349138]
- Rollema H, Chambers L, Coe J, Glowa J, Hurst R, Lebel L, Lu Y, Mansbach R, Mather R, Rovetti C. Pharmacological profile of the $\alpha 4 \beta 2$ nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. *Neuropharmacology.* 2007; 52:985–994. [PubMed: 17157884]
- Rukstalis M, Jepson C, Patterson F, Lerman C. Increases in hyperactive-impulsive symptoms predict relapse among smokers in nicotine replacement therapy. *J Subst Abuse Treat.* 2005; 28:297–304. [PubMed: 15925263]
- Schafer JL, Graham JW. Missing data: Our view of the state of the art. *Psychol Methods.* 2002; 7:147. [PubMed: 12090408]
- Shadish, WR., Cook, TD., Campbell, DT. Wadsworth Cengage learning. 2002. Experimental and quasi-experimental designs for generalized causal inference.
- Stapleton JA, Watson L, Spirling LI, Smith R, Milbrandt A, Ratcliffe M, Sutherland G. Varenicline in the routine treatment of tobacco dependence: A pre-post comparison with nicotine replacement therapy and an evaluation in those with mental illness. *Addiction.* 2008; 103:146–154. [PubMed: 18028247]
- Sullivan MA, Rudnik-Levin F. Attention deficit/hyperactivity disorder and substance abuse. Diagnostic and therapeutic considerations. *Ann NY Acad Sci.* 2001; 931:251–270. [PubMed: 11462745]
- Tercyak KP, Lerman C, Audrain J. Association of attention-deficit/hyperactivity disorder symptoms with levels of cigarette smoking in a community sample of adolescents. *J Am Acad Child Adolesc Psychiatry.* 2002; 41:799–805. [PubMed: 12108804]
- Tidey JW, Rohsenow DJ, Kaplan GB, Swift RM. Cigarette smoking topography in smokers with schizophrenia and matched non-psychiatric controls. *Drug Alcohol Depend.* 2005; 80:259–265. [PubMed: 15869844]
- USDHHS. Clinical practice guideline. U.S. Public Health Service; Rockville, MD: 2008. Treating tobacco use and dependence: 2008 update.
- Volkow ND, Wang GJ, Kollins SH, Wigal TL, Newcorn JH, Telang F, Fowler JS, Zhu W, Logan J, Ma Y, Pradhan K, Wong C, Swanson JM. Evaluating dopamine reward pathway in ADHD: Clinical implications. *JAMA.* 2009; 302:1084–1091. [PubMed: 19738093]
- Whitley HP, Moorman KL. Interference with smoking-cessation effects of varenicline after administration of immediate-release amphetamine-dextroamphetamine. *Pharmacotherapy.* 2007; 27:1440–1445. [PubMed: 17896898]
- Willcutt EG, Nigg JT, Pennington BF, Solanto MV, Rohde LA, Tannock R, Loo SK, Carlson CL, McBurnett K, Lahey BB. Validity of DSM-IV attention deficit/hyperactivity disorder symptom dimensions and subtypes. *J Abnorm Psychol.* 2012; 121:991–1010. [PubMed: 22612200]
- Zhang L, Dong Y, Doyon WM, Dani JA. Withdrawal from chronic nicotine exposure alters dopamine signaling dynamics in the nucleus accumbens. *Biol Psychiatry.* 2012; 71:184–191. [PubMed: 21872847]

Highlights

- The role of Attention-deficit/hyperactivity disorder (ADHD) symptoms in a pharmacological smoking cessation trial is examined
- Smoking cessation is associated with ADHD Hyperactivity/Impulsivity (HI) symptoms
- Varenicline reduced smoking and withdrawal in individuals with high HI symptoms
- Individuals with high HI symptoms in the placebo condition had the worst outcomes
- Varenicline's effects may differ in individuals with high vs. low HI symptoms

Figure 1. Changes in Mean Cigarettes Smoked Per Day across Assessment Time Point By Medication Condition and ADHD Hyperactive-Impulsive (HI) Symptoms

Figure shows unadjusted average cigarettes per day at each assessment time for individuals with higher and lower ADHD Hyperactive/Impulsive (HI) symptoms in the two treatment conditions. Individuals with ≥ 5 HI symptoms who received varenicline smoked the fewest cigarettes per day at the end of treatment (Week 12) and individuals with ≥ 5 HI symptoms who received the placebo treatment smoked the most cigarettes per day at the end of treatment (Week 12). At follow up (Week 36) the individuals with ≥ 5 HI symptoms who received placebo were smoking at the highest levels, over 9 cigs/day. In the placebo group, 59 individuals reported < 5 HI and 35 reported ≥ 5 HI symptoms. In the varenicline group, 69 individuals reported < 5 HI symptoms and 42 reported ≥ 5 HI symptoms.

Figure 2. Change in withdrawal as a mediator of treatment in individuals with high versus low hyperactivity-impulsivity (HI) symptoms

Standardized parameter estimates are presented. Parameter estimate before the slash is the low HI group, and the estimate after the slash is the high HI group (LOW/HIGH). Note. * $p < .05$; ** $p < .01$. There were 51 males (26 females) in the high ADHD HI group (mean age=32.53 SD =9.70) and 81 males (46 females; 1 missing) in the low ADHD HI group (mean age=35.01 SD =10.19).

Table 1

Subject Demographics by Medication Condition

	Varenicline n=111	Placebo n=94
	Mean (SD) or Number (%)	Mean (SD) or Number (%)
Age	34.22 (10.08)	34.02 (10.10)
Gender (male)	64.90%	63.80%
Race		
<i>American Indian/Alaska Native</i>	9.00%	10.90%
<i>Asian</i>	1.80%	0%
<i>African American</i>	3.60%	4.30%
<i>Native Hawaiian/Pacific Islander</i>	0.90%	0%
<i>White</i>	70.30%	70.70%
<i>Mixed</i>	14.40%	14.10%
Years Smoking	16.04 (10.19)	17.06 (9.96)
Baseline FTND (total 1–6)	4.5 (2.11)	4.57 (2.20)
ADH IN	3.72 (3.92)	3.18 (2.54)
ADH HI	4.21 (3.47)	4.38 (3.28)
Baseline BDI-II	2.79 (4.13)	3.06 (4.01)
Baseline BAI	2.70 (3.87)	2.39 (2.80)
Baseline Cigs/Day	14.61 (6.58)	14.83 (7.61)

Note. FTND = Fagerstrom Test for Nicotine Dependence; ADH IN = ADHD Symptom Checklist Inattention Subscore; ADH HI= ADHD Symptom Checklist Hyperactivity/Impulsivity Subscale. There were no significant differences between groups for any demographic, smoking, or ADHD variables.

Table 2

Associations of time, treatment, and ADHD symptom dimensions on average cigarettes per day during treatment and at follow up: Main effects and interactions from GEE models

	Average cigarettes per day			
ADHD Symptom Dimension	Estimate	(SE)	Z	P
<i>Hyperactivity-impulsivity (HI)</i>				
GEE fit criteria	QIC= -2118.8853			
Intercept	2.0786	0.2087	9.9600	<.0001
Time	-0.3416	0.0649	-5.2700	<.0001
Medication Condition	0.0662	0.1563	0.4200	0.6719
HI	-0.0114	0.0222	-0.5100	0.6071
Time X Medication ^a	-0.0360	0.0895	-0.4000	0.6875
Time X HI	0.0189	0.0108	1.7600	0.0787
Med X HI	-0.0031	0.0289	-0.1100	0.9134
Time X Med X HI	-0.0386	0.0169	-2.2800	0.0224
FTND	-0.0676	0.0920	-0.7400	0.4622
BDI-II	0.1213	0.0213	5.7000	<.0001
Age	0.0119	0.0116	1.0300	0.3046
Gender	0.0054	0.0139	0.3900	0.6969
<i>Inattention (IN)</i>				
GEE fit criteria	QIC= -2095.9072			
Intercept	2.1010	0.2033	10.3400	<.0001
Time	-0.2831	0.0639	-4.4300	<.0001
Medication Condition	0.0400	0.1488	0.2700	0.7881
IN	-0.0259	0.0297	-0.8700	0.3825
Time X Medication	-0.1542	0.0868	-1.7800	0.0756
Time X IN	0.0102	0.0165	0.6200	0.5346
Med X IN	0.0085	0.0341	0.2500	0.8031
Time X Med X IN	-0.0141	0.0205	-0.6900	0.4923
FTND	-0.0702	0.0931	-0.7500	0.4510
BDI-II	0.1220	0.0213	5.7200	<.0001
Age	0.0134	0.0118	1.1400	0.2555
Gender	0.0065	0.0143	0.4600	0.6466

Note. GEE= Generalized Estimating Equations; FTND=Fagerstrom Test for Nicotine Dependence; ADHD=Attention Deficit Hyperactivity Disorder; BDI-II=Beck Depression Inventory (II). In models without the Time X Medication X ADHD interaction term, the Time X Medication interaction reported in the parent trial (Littlewood et al., 2017) is significant. With the addition of the three-way interaction (the primary focus of our analysis) this effect drops to non-significance.