

Published in final edited form as:

*Drug Alcohol Depend.* 2012 August 1; 124(3): 268–273. doi:10.1016/j.drugalcdep.2012.01.019.

## Attention-deficit/hyperactivity Disorder (ADHD) Symptoms, Craving to smoke, and Tobacco Withdrawal Symptoms in Adult Smokers with ADHD

Ivan Berlin<sup>a,\*</sup>, Mei-Chen Hu<sup>b</sup>, Lirio S. Covey<sup>c</sup>, and Theresa Winhusen<sup>d</sup>

<sup>a</sup>Département de Pharmacologie, Hôpital Pitié-Salpêtrière-Faculté de médecine, Université P. & M. Curie - INSERM U894, 47, bd de l'Hôpital, 75013 Paris, France

<sup>b</sup>Department of Psychiatry, Columbia University, 1051 Riverside Drive, New York, NY 10032, United States

<sup>c</sup>New York State Psychiatric Institute, Columbia University Medical Center, 1051 Riverside Drive, New York, NY 10032, United States

<sup>d</sup>Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, 3210 Jefferson Avenue, Cincinnati, OH 45220, United States

### Abstract

**Background**—Tobacco withdrawal symptoms may be confounded with attention deficit/hyperactivity disorder (ADHD) symptoms among smokers with ADHD.

**Objective**—1) to assess overlap between ADHD symptoms and tobacco/nicotine withdrawal symptoms and craving; 2) to assess the relationship between craving or withdrawal symptoms and the effect of osmotic-release oral system methylphenidate (OROS-MPH) on ADHD symptoms; 3) to assess the association of ADHD symptoms, craving, and withdrawal symptoms with abstinence.

**Methods**—Secondary analysis of a randomized, placebo controlled smoking cessation trial assessing the efficacy of OROS-MPH taken in addition to nicotine patch among individuals with ADHD. ADHD symptoms, withdrawal symptoms, and craving were assessed at baseline and 2, 4 and 6 weeks after a target quit day.

**Results**—Withdrawal symptoms and craving showed limited and modest overlap with ADHD symptoms prior to abstinence but more extensive and stronger correlation after quit day. Compared to placebo, OROS-MPH reduced ADHD symptoms; this effect was attenuated by

---

© 2012 Elsevier Ireland Ltd. All rights reserved.

\*Correspondence Dr. I. Berlin, Département de Pharmacologie, Hôpital Pitié-Salpêtrière, 47, bd de l'Hôpital, 75013 Paris, France, ivan.berlin@psl.aphp.fr, Fax : +33 1 42 16 16 88, Phone : +33 1 42 16 16 78.

**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.

### Contributors

Ivan Berlin and Lirio Covey conceived and designed this secondary analysis, conducted the literature search, and wrote the manuscript. Mei-Chen Hu had full access to the data and performed the statistical analyses, with advice from Ivan Berlin and Lirio Covey. Theresa Winhusen was a co-principal investigator for the parent study. All authors contributed to the interpretation of findings and writing of the final version of this paper.

### Conflict of interest

Ivan Berlin received honoraria for advisory roles with Sanofi-Aventis and Pfizer, Inc. in the last 5 years. Lirio S. Covey received research support in 2009 from Pfizer, Inc. The other co-authors report no conflict of interest.

controlling for withdrawal symptoms, but not by craving. Craving, but not ADHD symptoms and withdrawal symptoms, was associated with abstinence during the trial.

**Conclusion**—When treating smokers with ADHD 1) craving, rather than tobacco withdrawal symptoms or ADHD symptoms may be the more effective therapeutic smoking cessation targets; 2) careful distinction of craving, withdrawal symptoms, and ADHD symptoms when assessing withdrawal phenomena is needed.

### Keywords

ADHD symptoms; nicotine withdrawal symptoms; craving to smoke; smoking cessation

## 1. Introduction

Tobacco smoking, nicotine/tobacco dependence and attention-deficit/hyperactivity disorder (ADHD) frequently co-occur. Persons with ADHD are more likely to become regular smokers (Pomerleau et al., 1995; Tercyak et al., 2002), begin smoking earlier, smoke more heavily (Kollins et al., 2005; Lambert et al., 2000), and may experience greater difficulty when trying to stop smoking (Humfleet et al., 2005; Covey et al., 2008) compared to persons without ADHD. Nicotine ameliorates inattentiveness and problems in response inhibition (Conners et al., 1996; Levin et al., 1996; Potter et al., 2004; Poltavski et al., 2006), which are core symptoms of ADHD. Nicotine can reduce the demonstrated deficits in dopaminergic function associated with ADHD (Volkow et al., 2007) suggesting a “self-medication” rationale for greater tobacco use among persons with ADHD (Gray and Upadhyaya, 2009).

The increased recognition that tobacco use and nicotine dependence are highly prevalent among persons with ADHD (Gray and Uphadyaya, 2009) has spurred investigations into details of the relationship between those disorders, such as the association between their symptom profiles. The core symptoms of ADHD (inattention, hyperactivity, and impulsiveness; APA, 2000) are conceptually and clinically similar to symptoms of nicotine withdrawal, such as difficulty concentrating, restlessness, and impatience (APA, 2000). A study of adolescent smokers that examined correlations during the non-abstinence phase of a smoking cessation treatment found significant correlations among several of the ADHD and the nicotine withdrawal symptoms (Gray et al., 2010). A 12-day abstinence trial conducted with adult, non-treatment seeking smokers, on the other hand, observed that withdrawal symptoms, which were experienced more severely by smokers with than without ADHD, were unrelated to changes in ADHD symptoms (McClernon et al., 2011).

To clarify relationships among smoking-related (i.e., withdrawal symptoms and craving) and ADHD-related symptoms, as well as their relevance to the efficacy of smoking cessation treatment for smokers with ADHD, we conducted secondary analyses of data from a trial of osmotic-release oral system methylphenidate (OROS-MPH) for smokers with ADHD (Winhusen et al., 2010). The parent trial was a randomized, placebo controlled trial that evaluated if OROS-MPH to treat ADHD, combined with smoking cessation treatment, increases smoking abstinence. The main results showed that OROS-MPH reduced ADHD symptoms but did not improve smoking abstinence rate (Winhusen et al., 2010).

Our objectives in the current analysis were: 1) to assess overlap between ADHD symptoms and nicotine withdrawal symptoms and craving; 2) to assess the relationship between craving or withdrawal symptoms and the OROS-MPH effect on ADHD symptoms; 3) to assess the association of ADHD symptoms, craving, and withdrawal symptoms with abstinence. Findings from these analyses could impact clinical decisions regarding the

manner, timing, and type of smoking cessation treatment when the smoker trying to quit also suffers from ADHD.

## 2. Methods

### 2.1. Design of the parent OROS-MPH trial

Briefly, this was a randomized, double-blind, placebo-controlled trial assessing the efficacy of OROS-MPH compared to placebo for increasing smoking cessation rate among adult smokers with ADHD when added to nicotine patch and counseling. The study design consisted of an 11-week treatment phase with a four-week pre-quit phase and seven weeks of a planned abstinence period. All participants received a thorough explanation of the study from the investigators and signed an informed consent form. The trial was conducted at six sites (Cambridge, Massachusetts; Columbus, Ohio; New York City, New York (2 sites); Portland, Oregon; Rochester, Minnesota) and approved by the Institutional Review Board at individual participating sites.

Participants were given 21 mg/24 hours nicotine patches from the target quit day (day 27) through week 11, received 14 mg/24 hours patches for study weeks 12 and 13, and 7 mg/24 hours patches for study week 14. Participants were randomized to OROS-MPH or matching placebo in a 1:1 ratio, with stratification by site, by a centralized, computerized system. For OROS-MPH the starting dose of 18 mg/day was escalated during the first two study weeks to a maximum of 72 mg/day or to the highest dose tolerated. Study participants received \$25 (\$15 at one site) per research visit; at the end-of-treatment visit (week 11) participants received an additional \$25. More details of the study protocol, methods, and procedures are provided in the main outcome paper (Winhusen et al., 2010).

### 2.2. Participants

Eligible participants were adults with ADHD who smoked at least 10 cigarettes per day, had an expired air carbon monoxide (CO) level  $\leq$  8 ppm, and smoked cigarettes regularly for at least 3 months prior to inclusion, wished to quit smoking, were in good physical health as determined by a medical history, electrocardiogram, vital signs and fulfilled DSM-IV criteria for ADHD as assessed by the Adult Clinical Diagnostic Scale version 1.2 (Adler and Cohen, 2004). The use of the parent study's data and analysis was approved by the IRB of the New York State Psychiatric Institute, Columbia University.

### 2.3. Measures

The ADHD Rating Scale (ADHD-RS; DuPaul et al., 1998; Adler and Cohen, 2004) was used to assess DSM-IV ADHD symptoms. This instrument contains 18 individual items, 9 each reflecting inattention and hyperactivity/impulsivity. Each item is rated on a 4-point scale (never or rarely: 0, sometimes: 1, often: 2, very often: 4). The total score can range from 0 to 54, the maximum score for both inattention and hyperactivity/impulsivity subscales is 27. Cronbach's  $\alpha$  for the ADHD-RS at baseline was 0.86 in this study. ADHD symptoms were assessed at baseline (three to four weeks before a target quit date), and at weeks 2, 4, and 6 after the target quit date.

Tobacco withdrawal symptoms and craving were assessed with the Minnesota Withdrawal Symptom Scale (MNWS) (Hughes and Hatsukami 1986) at baseline and at weeks 2, 4, and 6 after quit day. Although DSM-IV does not include craving for smoking as a withdrawal symptom, we examined the "desire to smoke" item in the MNWS, referred to in the literature and in this paper as "craving." Craving was assessed separately from the seven other MNWS items (anger/irritability, anxiety/nervousness, difficulty concentrating,

impatience/restlessness, hunger, awakening at night, and depression). Cronbach's  $\alpha$  for the tobacco withdrawal symptoms at baseline was 0.78.

Smoking abstinence was assessed as 7-day point-prevalence abstinence as reported at clinic visits on weeks 2, 4, and 6 after quit day by participants' self-report verified by expired carbon monoxide 8 parts per million. Continuous abstinence (no slips or lapses from quit day) was treated as a time-varying variable in the models only for completers (showed up at weeks 2, 4 and 6 after quit day), defined as point-prevalence abstinence at week 2 for post-quit week 2, abstinence at both weeks 2 and 4 for post quit week 4, and abstinence at weeks 2, 4, 6 for post-quit week 6.

## 2.4. Data analysis

To assess the relationships between total and individual symptoms of ADHD, withdrawal symptoms, and craving, we used partial correlation coefficients (Pearson's  $r$ ), controlling for age, gender, race/ethnicity, site, and treatment. We adjusted for gender, based on prior research that showed its relationship with withdrawal symptoms (McClernon et al., 2011), and for race/ethnicity (white vs. nonwhite) based on prior evidence of its association with craving and abstinence (Covey et al., 2010). We applied generalized linear models (GLM) to investigate the effects of withdrawal symptoms and craving on total ADHD scores across the weeks of assessment, and time (before quit day vs. post-quit day). We performed separate models to test the association of withdrawal symptoms and craving with ADHD symptoms. Because a site effect has been demonstrated (Covey et al., 2011), it was tested as an additional fixed effect in the models. For the exploratory correlational analyses,  $p$ -values  $\leq 0.01$  were considered as significant to reduce likelihood of type 1 error due to multiple testing. To investigate their associations with total ADHD scores during the post-quit period, the effect of treatment, smoking abstinence, withdrawal symptoms and craving was tested on a stepwise manner in the GLM models, controlling for nicotine patch compliance and OROS-MPH (vs. placebo) compliance. In order to test whether the associations between ADHD and withdrawal symptoms or craving differed by treatment, the possible interactions among treatment and withdrawal symptoms or craving were tested. The association of total ADHD scores, withdrawal symptoms, and craving with smoking abstinence were also investigated using GLM models. The GLM methodology was able to handle within-subject correlations (Little and Rubin, 1987; Diggle et al., 2004). PROC Glimmix in SAS (SAS 9.2) was used to conduct the analyses.

## 3. Results

### 3.1. Characteristics of the sample

The total sample consisted of 255 smokers with ADHD. The mean age was 37.8 years ( $SD=10$ , range: 19 to 56); 56.5 % of the sample was male, 34.1 % were married, 22.4 % were divorced or separated and 43.9 % were single; 79.2 % were non-Hispanic Whites, 13.7 % African Americans and 6.3 % Hispanics. The mean age at starting smoking was 13.8 years ( $SD=3$ , range: 5 to 27). The mean number of cigarettes smoked per day was 20.2 ( $SD=10$ , range: 10 to 60). The mean number of years of education was 14.4 years ( $SD=2.4$ , range: 6 to 24). One hundred eighty four smokers showed up at each post-quit date visit (weeks 2, 4 and 6) and were defined as a completer sample; the distributions of demographic and smoking data in the total and the completer samples were similar.

### 3.2. Associations between total ADHD symptoms, total tobacco withdrawal symptoms, and craving at baseline and during the post-quit period

Table 1 shows the means and standard deviations at baseline and during the post-quit clinic visits for the total ADHD symptoms, total nicotine withdrawal scores, and craving, and

partial correlation coefficients between ADHD symptoms and the withdrawal and craving measures. Mean scores on the three measures declined during the study. The partial correlation coefficients between ADHD symptoms and withdrawal symptoms, significant at all time points, were substantially higher after the quit date than at baseline. For craving, the correlations with ADHD symptoms were not significant at baseline, but increased to statistical significance at weeks 2 to 6 after quit day.

A Glimmix model on ADHD symptoms did not show significant effects of age, gender, or race/ethnicity (all  $p$ -values  $>0.10$ ). The association between withdrawal symptoms and ADHD symptoms after quit day was significantly stronger than before the quit day ( $\beta = 0.46$ ,  $s.e.=0.11$ ,  $p < 0.0001$ ). As in the correlational analysis, the Glimmix model showed a significant association between ADHD-RS scores and withdrawal symptoms at baseline ( $\beta = 0.36$ ,  $s.e.= 0.09$ ,  $p < 0.0001$ ) and after quit day ( $\beta = 0.82$ ,  $s.e.= 0.07$ ,  $p < 0.0001$ ). Also consistent with the correlational analysis, there was no association between craving and ADHD symptoms at baseline ( $\beta = 0.34$ ,  $s.e.=0.77$ ,  $p = 0.66$ ) but a significant association occurred after quit day ( $\beta = 1.74$ ,  $s.e.=0.32$ ,  $p < 0.0001$ ). However, the effect of the time by craving interaction term was not significant ( $\beta = 1.40$ ,  $s.e.=0.81$ ,  $p = 0.09$ ).

### 3.3. Associations between individual withdrawal symptoms, individual ADHD symptoms, and craving

Table 2 explores the correlations of individual ADHD symptoms with craving and withdrawal symptoms at baseline and on the second week after quit day (similar correlations as seen at week 2 were seen at weeks 4 and 6). At baseline, significant correlations of individual ADHD symptoms with craving as well as with individual withdrawal symptoms were few and small in magnitude. These included correlations between impatience/restlessness with five of the hyperactivity/impulsivity symptoms, and between anger/irritability with difficulty sustaining attention. At the second week after quit day, more numerous significant and stronger correlations between withdrawal and ADHD symptoms were evident. These included significant correlations between individual withdrawal symptoms and several ADHD items, i.e., all 18 ADHD symptoms with impatience/restlessness, 17 with difficulty concentrating, 16 with anxiety/nervousness, 14 with anger/irritability, 10 with depression, and 5 with awakening at night. Hunger, a withdrawal symptom not putatively associated with ADHD, did not show a correlation with any ADHD symptom at any time during the trial. No correlations between craving and any of the ADHD symptoms were observed at baseline; after quit day, a number of significant correlations between craving and several ADHD symptoms (5 inattentive and 1 hyperactivity symptoms) were observed.

### 3.4. Withdrawal symptoms, craving, and treatment effects on ADHD symptoms during the post-quit period

The basic Glimmix model on ADHD symptoms (Table 3) during the post-quit period showed a significant treatment effect, i.e., ADHD scores decreased more on OROS-MPH than on placebo ( $\beta = -6.05$ ,  $s.e. = 1.38$ ,  $p < 0.001$ ). Abstinence status was not associated with ADHD scores. Addition of withdrawal symptoms to the basic model showed that both withdrawal symptoms and treatment were significantly associated with ADHD symptoms. In order to test whether the associations between ADHD and withdrawal symptoms or craving differed by treatment, interaction terms were entered in a Glimmix model. The only significant interaction was that between treatment and withdrawal symptoms ( $F(1, 378) = 7.12$ ,  $p < 0.01$ ). The association of withdrawal symptoms with ADHD scores was significantly stronger among patients on OROS-MPH ( $\beta = 0.73$ ,  $s.e.=0.09$ ,  $p < 0.0001$ ) than among patients on placebo ( $\beta = 0.38$ ,  $s.e.=0.13$ ,  $p < 0.01$ ).

Compared to OROS-MPH's effect on ADHD scores in the absence of withdrawal symptoms, inclusion of withdrawal symptoms was associated with a decreased effect of OROS-MPH of about 26% ( $=(-6.05-(-4.50))/(-6.05)$ ) on ADHD symptoms. Addition of craving to the basic model continued to show a treatment effect on ADHD symptoms ( $\beta = -5.98$ ,  $s.e.=1.36$ ,  $p<0.001$ ), but no significant effect of craving ( $\beta = 0.35$ ,  $s.e.=0.30$ ,  $p=0.25$ ) was observed.

### 3.5. Association of craving, withdrawal symptoms, and ADHD symptoms with smoking abstinence

When craving, withdrawal symptoms, and ADHD symptoms were included in a model that controlled for all potential confounders and also for compliance with nicotine patch and OROS-MPH/placebo treatment (Table 4), the only variable significantly and inversely associated with abstinence status was craving ( $\beta = -0.79$ ,  $s.e.=0.14$ ,  $p<0.0001$ ). In a stepwise analysis, withdrawal symptoms appeared to influence abstinence ( $\beta = -0.08$ ,  $s.e.=0.03$ ,  $p=0.0075$ ), but when the effect of craving was controlled for, the association of withdrawal symptoms with abstinence was no longer significant ( $p=0.97$ ). The same results were observed for continuous abstinence among completers (data not shown).

## 4. Discussion

This secondary analysis of data from a smoking cessation trial demonstrated little correlation between ADHD symptoms and the tobacco-related symptoms of craving and withdrawal before quit day. However, during the post-quit period, significant overlap between ADHD symptoms and nicotine withdrawal symptoms, and to a lesser extent, craving, became apparent. As reported earlier (Winhusen et al., 2010), we observed an effect of OROS-MPH on ADHD symptoms; in the present analysis we found that OROS-MPH also reduced nicotine withdrawal symptoms, but not craving to smoke. Confirming results from a previous analysis (Covey et al, 2010), craving, but not symptoms of ADHD or nicotine withdrawal was associated with abstinence. Assessment of compliance with the treatment regimen (nicotine patch and OROS-MPH/Placebo) did not alter the observed relationships.

Studies have shown that smokers with ADHD experience withdrawal symptoms more severely than do smokers without ADHD (McClernon et al., 2008; 2011). The present study revealed significant correlations between ADHD and withdrawal symptoms during the post-quit phase and, thus, the differences previously reported between smokers with and without ADHD may reflect a confounding between ADHD and withdrawal symptoms.

The present analysis has demonstrated that in adult smokers with ADHD who undergo smoking cessation treatment, nicotine withdrawal symptoms and ADHD symptoms weakly overlap prior to abstinence but may be confounded during the post-quit period. This finding implies the need for careful interpretation of nicotine withdrawal symptoms, both before and after the quit day, as the reported symptoms may be indicative of a co-occurring condition, such as ADHD. As suggested by Gray et al. (2010), it may be necessary to develop specific measures that are not confounded by ADHD symptoms to accurately assess smoking cessation progress in the presence of ADHD. Our two-fold finding of increased correlation between withdrawal symptoms and ADHD symptoms following quit day, and the lack of predictive effect of withdrawal symptoms on abstinence (upon controlling for craving) contrasts with findings by McClernon and colleagues (2011). These authors observed that withdrawal symptoms were associated with abstinence, and this association was unrelated to ADHD symptoms. The difference in observations could result from methodological differences between the 12-day trial (McClernon et al., 2011) and our parent OROS-MPH trial (Winhusen et al., 2010): 1) the post-quit period was 7-weeks in our study and only 12

days in the study by McClernon et al.; 2) study participants in our study had entered the trial seeking to stop smoking whereas only smokers who were not planning to stop smoking entered the 12-day trial; 3) a specific association of craving with withdrawal symptoms and their combined association with abstinence was not evaluated in the 12-day trial, 4) the withdrawal measure used by McClernon and colleagues (2011), the Shiffman-Jarvik Withdrawal Questionnaire (SJWQ), described as a “32-item measure of craving,” may have captured elements of the addiction process that were better reflective of craving than the items included in the MNWS.

There was a significant interaction effect of treatment and withdrawal symptoms on ADHD symptoms but no treatment by craving interaction effect was observed. Thus, ADHD symptoms were associated with both OROS-MPH and withdrawal symptoms but not with craving. The irregular association of craving with ADHD symptoms (no craving-ADHD symptoms association at baseline, inconsistent association after quit day) may simply reflect the parallel evolution of craving with withdrawal symptoms. The association between withdrawal symptoms and ADHD symptoms was stronger with OROS-MPH than with placebo, which likely reflects reduced variance from OROS-MPH acting on similar ADHD and withdrawal symptoms.

Amelioration of the ADHD and withdrawal symptoms with OROS-MPH did not result in successful smoking cessation among the participants in the present study (Covey et al., 2010; Winhusen et al., 2010); rather, it was reduction in craving to smoke, which was irregularly associated with both withdrawal symptoms and ADHD symptoms (as shown in Tables 1 and 2) that facilitated smoking cessation. Withdrawal symptoms showed significant correlation with ADHD symptoms and abstinence but inclusion of craving nullified the withdrawal symptoms – abstinence association. Withdrawal symptoms may be uncertain predictors of abstinence because their association with smoking abstinence is confounded by craving. This may explain also why ADHD symptoms, which do not tap craving, were not associated with abstinence status.

The limited correlation between craving and ADHD symptoms, along with the demonstrated influence of craving on abstinence (Covey et al., 2010), may help to explain why, despite its record as an efficacious medication for alleviating symptoms of ADHD (McBurnett and Starr, 2011), OROS-MPH did not increase smoking cessation rates in the present sample of smokers with ADHD (Winhusen et al., 2010). Nicotine has been found to reduce ADHD symptoms (Gehricke et al., 2009) and ADHD medications reduce nicotine withdrawal symptoms in smokers with ADHD (Gehricke et al., 2011). However, ADHD medications do not seem to reduce craving to smoke (Gehricke et al., 2011), a core predictor of successful smoking cessation (Dawkins et al., 2009; Berlin et al., 2010). The lack of a significant OROS-MPH effect on craving may not generalize to the effects that would be observed with immediate release methylphenidate (IR MPH). Specifically, laboratory findings have shown that IR MPH significantly increases smoking in adult smokers without ADHD who are not trying to quit smoking (Rush et al., 2005; Vansickel et al., 2007) and, thus, might serve to increase craving. Thus, medications acting on craving may be a promising smoking cessation for smokers with ADHD.

A primary strength of the present study is the evaluation of smokers with ADHD who wanted to quit smoking and were studied prior to and after their quit attempt, which more closely reflects the clinical setting compared to the studies by Gray et al. (2010) and McClernon et al. (2011) that sought to evaluate the relationship between nicotine withdrawal and ADHD. However, this was a secondary, post-hoc analysis of a randomized therapeutic trial; thus, further studies specifically planned for investigating the overlap between ADHD and nicotine withdrawal symptoms are needed to confirm the current

findings. Similarly, prospective studies are needed to confirm the lack of association between ADHD symptoms and smoking abstinence and the potential predictive role of craving in successful quitting in this specific population. The generalizability of the findings warrant caution because of the evident selection bias characterizing clinical therapeutic trials.

In conclusion, among smokers with ADHD, ADHD symptoms and nicotine withdrawal symptoms may overlap, in particular, after quitting smoking. Craving to smoke but not ADHD or nicotine withdrawal symptoms is associated with smoking abstinence. Reduction of craving may help smokers with ADHD quit.

## Acknowledgments

### Role of funding source

This study was supported by the following grants from the National Institute on Drug Abuse (NIDA): U10-DA015831 and K24 DA022288 to Harvard University; U10-DA013035 and K24 DA022412 to New York State Psychiatric Institute; U10-DA013046 to New York University; U10-DA013036 to Oregon Health and Science University; U10-DA013732 to the University of Cincinnati. Lirio Covey received support for this secondary analysis from U10-DA013732S3 and U10-DA013035. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Drug Abuse or the National Institute of Health. McNeil Consumer & Specialty Pharmaceuticals provided the study medication and matching placebo at no cost. McNeil Pharmaceuticals had no role in the study design, in the analysis and interpretation of data, or in the writing of the report.

## References

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition, Text Revision. Washington DC: American Psychiatric Association; 2000.
- Adler L, Cohen J. Diagnosis and evaluation of adults with attention-deficit/ hyperactivity disorder. *Psychiatr. Clin. N. Am.* 2004; 27:187–201.
- Berlin I, Jacob N, Coudert M, Perriot J, Schultz L, Rodon N. Adjustment of nicotine replacement therapies according to saliva cotinine concentration: the ADONIS trial. A randomized study in smokers with medical comorbidities. *Addiction.* 2011; 106:833–843. [PubMed: 21205047]
- 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]
- 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]
- Covey LS, Hu MC, Winhusen T, Weissman J, Berlin I, Nunes EV. OROS-methylphenidate or placebo for adult smokers with attention deficit hyperactivity disorder: racial/ethnic differences. *Drug Alcohol Depend.* 2010; 110:156–159. [PubMed: 20219292]
- Covey LS, Hu MC, Green CA, Brigham G, Hurt RD, Adler L, Winhusen T. An exploration of site effects in a multisite trial of OROS-methylphenidate for smokers with attention deficit/ hyperactivity disorder. *Am. J. Drug Alcohol Abuse.* 2011; 37:392–399. [PubMed: 21854282]
- Dawkins L, Powell JH, Pickering A, Powell J, West R. Patterns of change in withdrawal symptoms, desire to smoke, reward motivation and response inhibition across 3 months of smoking abstinence. *Addiction.* 2009; 104:850–858. [PubMed: 19344444]
- Diggle, PJ.; Liang, KY.; Zeger, SL. Analysis of longitudinal data. Oxford, UK: Oxford University Press; 2004.
- DuPaul, GJ.; Power, TJ.; Anastopoulos, AD.; Reid, R. ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation. New York: Guilford Press; 1998.
- Gehricke JG, Hong N, Wigal TL, Chan V, Doan A. ADHD medication reduces cotinine levels and withdrawal in smokers with ADHD. *Pharmacol. Biochem. Behav.* 2011; 98:485–491. [PubMed: 21356232]



- Gehricke JG, Hong N, Whalen CK, Steinhoff K, Wigal TL. Effects of transdermal nicotine on symptoms, moods, and cardiovascular activity in the everyday lives of smokers and nonsmokers with attention-deficit/hyperactivity disorder. *Psychol. Addict. Behav.* 2009; 23:644–655. [PubMed: 20025370]
- Gray KM, Baker NL, Carpenter MJ, Lewis AL, Upadhyaya HP. Attention-deficit/ hyperactivity disorder (ADHD) confounds nicotine withdrawal self-report in adolescent smokers. *Am. J. Addict.* 2010; 19:325–331. [PubMed: 20653639]
- Gray KM, Upadhyaya HP. Tobacco smoking in individuals with attention-deficit/hyperactivity disorder: epidemiology and pharmacological approaches to cessation. *CNS Drugs.* 2009; 1:661–668. [PubMed: 19594195]
- Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch. Gen. Psychiatry.* 1986; 43:289–294. [PubMed: 3954551]
- Humfleet GL, Prochaska JJ, Mengis M, Cullen J, Muñoz 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 SC, McClernon J, 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]
- Lambert NM, Hartsough CS. Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants. *J. Learn. Disabil.* 2000; 33:314–316. [PubMed: 15493092]
- Levin ED, Conners CK, Sparrow E. Nicotine effects on adults with attention-deficit/ hyperactivity disorder. *Psychopharmacology (Berl.)*. 1996; 123:55–63. [PubMed: 8741955]
- Little, R.; Rubin, D. *Statistical Analysis with Missing Data*. New York: Wiley; 1987.
- McBurnett K, Starr HL. OROS methylphenidate hydrochloride for adult patients with attention deficit/ hyperactivity disorder. *Expert Opin. Pharmacother.* 2011; 12:315–324. [PubMed: 21226641]
- 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]
- McClernon FJ, Kollins SH, Lutz AM, Fitzgerald DP, Murray DW, Redman C, Rose JE. Effects of smoking abstinence on adult smokers with and without attention deficit hyperactivity disorder: results of a preliminary study. *Psychopharmacol. (Berl.)*. 2008; 197:95–105.
- Pomerleau OF, Downey KK, Stelson FW, Pomerleau CS. Cigarette smoking in adult patients diagnosed with attention deficit hyperactivity disorder. *J. Subst. Abuse.* 1995; 7:373–378.
- Poltavski DV, Petros T. Effects of transdermal nicotine on attention in adult nonsmokers with and without attention deficits. *Physiol. Behav.* 2006; 87:614–624. [PubMed: 16466655]
- Potter AS, Newhouse PA. Effects of acute nicotine administration on behavioral inhibition in adolescents with attention-deficit hyperactivity disorder. *Psychopharmacology.* 2004; 176:182–194. [PubMed: 15083253]
- Rush CR, Higgins ST, Vansickel AR, Stoops WW, Lile JA, Glaser PE. Methylphenidate increases cigarette smoking. *Psychopharmacology.* 2005; 181:781–789. [PubMed: 15983792]
- 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]
- Vansickel AR, Stoops WW, Glaser PEA, Rush CR. A pharmacological analysis of stimulant-induced increases in smoking. *Psychopharmacology.* 2007; 193:305–313. [PubMed: 17447052]
- Volkow ND, Wang GJ, Newcorn J, Telang F, Solanto MV, Fowler JS, Logan J, Ma Y, Schulz K, Pradhan K, Wong C, Swanson JM. Depressed dopamine activity in caudate and preliminary evidence of limbic involvement in adults with attention-deficit/hyperactivity disorder. *Arch. Gen. Psychiatry.* 2007; 64:932–940. [PubMed: 17679638]
- Winhusen TM, Somoza EC, Brigham GS, Liu DS, Green CA, Covey LS, Croghan IT, Adler LA, Weiss RD, Leimberger JD, Lewis DF, Dorer EM. Impact of attention-deficit/hyperactivity

disorder (ADHD) treatment on smoking cessation intervention in ADHD smokers: a randomized, double-blind, placebo-controlled trial. *J. Clin. Psychiatry.* 2010; 71:680–1688.

**Table 1**

Two-sided correlation coefficients between ADHD-RS scores and nicotine/tobacco withdrawal symptoms, craving, at baseline and during post-quit periods.<sup>a</sup> N=245

ADHD	Mean (SD)	Withdrawal symptoms				Craving			
		Baseline	Week 2 post quit	Week 4 post quit	Week 6 post quit	Baseline	Week 2 post quit	Week 4 post quit	Week 6 post quit
Mean (SD)		12.04 (5.49)	9.14 (5.71)	8.21 (5.49)	7.48 (5.32)	3.23 (0.67)	2.09 (1.27)	1.87 (1.25)	1.81 (1.26)
Baseline	36.36 (7.29)	0.23*				0.08			
Week 2 post quit	22.85 (12.46)		0.47*				0.26*		
Week 4 post quit	22.19 (12.76)			0.47*				0.34*	
Week 6 post quit	21.35 (12.56)				0.45*				0.25*

<sup>a</sup> Adjusted for age, gender, race/ethnicity, site and treatment group.

\* p<0.01 (two-sided).

ADHD-RS: Attention-Deficit/Hyperactivity Disorder Rating Scale

Table 2

Partial correlation coefficients between individual ADHD symptoms, craving, and individual nicotine/tobacco withdrawal symptoms at baseline and week 2 post quit date. N=245 (Standard characters: Baseline; Italics: Week 2 post-quit date) <sup>a</sup>

	Craving for cigarettes	Depression	Anger, Irritability	Anxiety, Nervousness	Difficulty concentrating	Impatience, Restlessness	Hunger	Awakening at night
<b>Inattention</b>								
Carelessness	.02 <i>.19*</i>	.04 <i>.16</i>	-.01 <i>.19*</i>	.07 <i>.29*</i>	.10 <i>.47*</i>	.08 <i>.39*</i>	-.005 <i>.03</i>	.05 <i>.09</i>
Difficulty sustaining attention	.07 <i>.18</i>	.07 <i>.22*</i>	.18* <i>.28*</i>	.12 <i>.30*</i>	.15 <i>.49*</i>	.15 <i>.43*</i>	.05 <i>.07</i>	.04 <i>.16</i>
Doesn't listen	.05 <i>.27*</i>	.04 <i>.21*</i>	.16 <i>.25*</i>	.11 <i>.30*</i>	.09 <i>.37*</i>	.10 <i>.42*</i>	.02 <i>.07</i>	.02 <i>.12</i>
No follow through	.04 <i>.21*</i>	.17 <i>.22*</i>	.14 <i>.23*</i>	.09 <i>.31*</i>	.05 <i>.44*</i>	.10 <i>.39*</i>	.08 <i>.09</i>	.05 <i>.22*</i>
Can't organize	.13 <i>.27*</i>	.07 <i>.18</i>	-.03 <i>.27*</i>	-.08 <i>.28*</i>	.14 <i>.47*</i>	.04 <i>.38*</i>	.01 <i>.04</i>	.06 <i>.16</i>
Avoids/dislikes tasks requiring sustained mental effort	.08 <i>.18</i>	.14 <i>.17</i>	.09 <i>.19*</i>	.07 <i>.24*</i>	.16 <i>.33*</i>	.15 <i>.34*</i>	.03 <i>.01</i>	.07 <i>.15</i>
Loses important items	.13 <i>.18</i>	.04 <i>.20*</i>	.04 <i>.21*</i>	.09 <i>.31*</i>	.06 <i>.37*</i>	.13 <i>.34*</i>	.07 <i>.09</i>	.08 <i>.22*</i>
Easily distractible	.06 <i>.16</i>	.12 <i>.19*</i>	.07 <i>.22*</i>	.05 <i>.29*</i>	.06 <i>.40*</i>	.06 <i>.38*</i>	.08 <i>.03</i>	.05 <i>.15</i>
Forgetful in daily activities	-.08 <i>.25*</i>	.06 <i>.23*</i>	.09 <i>.23*</i>	-.001 <i>.27*</i>	.01 <i>.43*</i>	.08 <i>.39*</i>	.13 <i>.11</i>	.002 <i>.13</i>
<b>Hyperactivity/impulsivity</b>								
Squirms and fidgets	.05 <i>.12</i>	.11 <i>.11</i>	.10 <i>.17</i>	.07 <i>.24*</i>	.05 <i>.37*</i>	.19* <i>.36*</i>	.08 <i>.05</i>	.06 <i>.15</i>
Can't stay seated	.03 <i>.15</i>	.06 <i>.20*</i>	.11 <i>.18</i>	.16 <i>.31*</i>	.21* <i>.33*</i>	.24* <i>.35*</i>	.01 <i>.09</i>	.10 <i>.22*</i>
Runs/climbs excessively (restless)	.07 <i>.23*</i>	.11 <i>.33*</i>	.13 <i>.33*</i>	.14 <i>.48*</i>	.13 <i>.37*</i>	.20* <i>.51*</i>	.12 <i>.14</i>	.06 <i>.29*</i>
Can't play/work quietly	-.1 <i>.15</i>	.02 <i>.23*</i>	.10 <i>.24*</i>	.16 <i>.36*</i>	.13 <i>.29*</i>	.11 <i>.34*</i>	.06 <i>.03</i>	-.01 <i>.08</i>

	Craving for cigarettes	Depression	Anger, Irritability	Anxiety, Nervousness	Difficulty concentrating	Impatience, Restlessness	Hunger	Awakening at night
On the go, driven by a motor	.001 .15	.12 <b>.20*</b>	.13 .18	.14 <b>.35*</b>	<b>.21*</b> <b>.31*</b>	<b>.20*</b> <b>.36*</b>	.08 .11	.06 .18
Talks excessively	.07 .04	.03 .04	.03 .06	.001 .06	.10 .10	.04 <b>.21*</b>	.08 -.05	-.01 .08
Blurts out answers	.003 .16	.003 .08	.08 <b>.20*</b>	.03 <b>.20*</b>	.06 <b>.25*</b>	.06 <b>.31*</b>	-.01 .04	.01 .11
Can't wait for turn	.04 .14	-.02 .16	.08 <b>.23*</b>	.11 <b>.24*</b>	.15 <b>.36*</b>	<b>.18*</b> <b>.32*</b>	.05 .06	.05 <b>.22*</b>
Intrudes/interrupts others	.1 .07	.001 .08	.04 <b>.20*</b>	.05 .17	.07 <b>.34*</b>	.08 <b>.29*</b>	.03 .01	-.08 .13

<sup>a</sup> Adjusted for age, gender, treatment group, site, and race/ethnicity

<sup>b</sup> Bold numbers: p<0.01, two-sided.

ADHD: attention-deficit/hyperactivity disorder

**Table 3**

Model results of the association of ADHD symptoms score with treatment, nicotine withdrawal symptoms, craving to smoke and abstinence status after target quit date (weeks 2, 4 and 6 post-quit).

	$\beta$ (s.e.)				
	Basic model <sup>a</sup>	Basic model plus withdrawal	Basic model plus interaction OROS-MPH (vs.placebo) and withdrawal	Basic model plus interaction OROS-MPH (vs.placebo) and craving	Basic model plus interaction OROS-MPH (vs.placebo) and craving
Abstinence	0.28 (0.72)	0.41 (0.71)	0.42 (0.71)	0.14 (0.76)	0.13 (0.76)
OROS-MPH (vs. placebo)	-6.05** (1.38)	-4.50* (1.26)	-7.36** (1.65)	-5.98** (1.36)	-5.40* (1.76)
Withdrawal symptoms		0.55** (0.07)	0.38** (0.09)		
Interaction between OROS-MPH (vs. placebo) and withdrawal			0.35* (0.13)		
Craving				0.35 (0.30)	0.50 (0.41)
Interaction between OROS-MPH (vs. placebo) and craving					-0.30 (0.58)

\* p<0.001,

\*\* p<0.0001

<sup>a</sup> Adjusted for age, gender, race, treatment, week of assessment, site, nicotine patch compliance, osmotic-release oral system methylphenidate (OROS-MPH) vs. placebo compliance, and baseline ADHD score.

ADHD: attention-deficit/hyperactivity disorder

**Table 4**

Association of ADHD symptoms score, treatment, nicotine withdrawal symptoms and craving to smoke with smoking abstinence after target quit date (weeks 2, 4 and 6 post-quit).

	Basic model <sup>a</sup>	Basic model plus withdrawal symptoms	Basic model plus withdrawal and craving
	$\beta$ (s.e.)		
Total ADHD symptoms	-0.01 (0.01)	0.01 (0.01)	0.004 (0.01)
OROS-MPH (vs. placebo)	0.17 (0.34)	0.02 (0.34)	0.08 (0.34)
Withdrawal symptoms		-0.08 (0.03) *	-0.002 (0.04)
Craving			-0.79 (0.14) **

\*  
p<0.01,

\*\*  
p<0.0001

<sup>a</sup>. Adjusted for age, gender, race, treatment, week of assessment, site, nicotine patch compliance, and osmotic-release oral system methylphenidate (vs. placebo) compliance.

ADHD: attention-deficit/hyperactivity disorder