EDITORIAL

Clin. Invest. (2013) 3(6), 1-xxx



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¹Center for Alcohol and Addition Studies, Department of Psychiatry and Human Behavior, Warren Alpert Medical School, Brown University, Providence, RI, USA

²Division of Behavioral Genetics, Department of Psychiatry, Rhode Island Hospital, Providence, RI, USA

³University of Southern California, Keck School of Medicine, Departments of Preventive Medicine and Psychology, Los Angeles, CA 90033, USA *Author for correspondence: Tel.: +1 323 442 2732 Fax: +1 323 442 2359 E-mail: adam.leventhal@usc.edu

The importance of considering ADHD in smoking cessation clinical trials

CLINICA

IVESTIGAT

L Cinnamon Bidwell^{1,2} & Adam M Leventhal*³

Tobacco use is a leading cause of preventable death worldwide. A large proportion of smokers are motivated to quit smoking and there are a number of available treatments that can increase quit rates [1]. However, relapse to smoking is common, with only 10-40% achieving long-term abstinence even after undergoing intensive treatment [1]. Hence, there continues to be a critical need for the development of novel smoking cessation treatments and clinical trials to empirically test the efficacy of attention deficit/hyperactivity disorder (ADHD) treatments.

While the literature has been instrumental in providing clear guidelines for statistical analysis and measurement of outcomes and mediators in smoking cessation clinical trials [2,3], less attention has been paid to patient characteristics, such as psychiatric disorders, which are clinically important to smoking cessation processes. ADHD – a common and disabling behavioral condition in both children and adults [4] – is strongly associated with nicotine dependence [5]. Importantly, ADHD may heighten risk for persistent smoking and poorer smoking cessation outcomes [6.7]. However, ADHD is rarely assessed or targeted in smoking cessation trials.

The aim of this editorial is to highlight the importance of considering ADHD in smoking cessation clinical trials. Below, we describe ADHD symptomatology, assessment, and clinical issues related to smoking and cessation processes, with the goal of providing guidance for smoking cessation research. It is our hope that the following discussion will stimulate heightened consideration of ADHD in smoking cessation clinical trials, which we feel will ultimately advance the science of smoking cessation more broadly.

Measurement, diagnosis & epidemiology of ADHD

According to the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* (DSM-IV), ADHD is classified by the presentation of six or more symptoms of inattention (IN) and/or six 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 [8]. While primarily defined as a disorder that onsets in childhood, ADHD symptoms persist into adolescence and adulthood, with recent meta-analyses estimating the population prevalence of diagnosable clinical ADHD is similar in children (5.7%) and adults (5.0%) [9,10]. The IN and HI symptom dimensions are used to define three ADHD subtypes: a predominantly inattentive type; a predominantly hyperactive–impulsive type; and a combined type. However, given that there is strong evidence to suggest that ADHD may exist on the extreme end of a continuum of attentional processes and hyperactive/impulsive behavior

Keywords: comorbidity • hyperactivity-impulsivity • inattention • nicotine • relapse prevention • withdrawal



[11], many researchers have advocated for analyzing continuous measures of ADHD symptoms rather than categorical diagnoses. Indeed, prior research in nonclinical samples of smokers suggests a linear relationship between increasing levels of current ADHD symptoms and important smoking outcomes in adults [12]. Furthermore, there is strong evidence that the IN and HI symptom dimensions of ADHD fall into empirically distinguishable factors with distinct impairment profiles [13]. In fact, there may be differential impacts of IN and HI on smoking trajectories and outcomes [14,15]. Thus, in order to measure ADHD in an optimal fashion, smoking researchers should strongly consider both linear measurement of ADHD symptoms and distinguishing between the two ADHD symptom dimensions.

Rating scales, augmented by clinical interview, can be an efficient means of collecting information regarding both ADHD symptoms and resulting clinical impairment. The commercially available Connors Adult ADHD Rating Scale, considered the gold standard of adult ADHD rating scales [16], yields dimensional ADHD index scores as well as DSM-IV-based symptom counts and has six different self- and observerreport formats of varying lengths. A publically available option is the Adult ADHD Rating Scale, which is a self-report scale derived from DSM-IV symptoms with high concurrent validity (intra-class correlation coefficient: 0.84) with clinician administered interviews [17]. It may also be useful to collect objective behavioral measures of attentional and inhibitory deficits pathognomonic of ADHD, such as the Continuous Performance Test and measures of delay discounting [18-21]. While these measures do not have sufficient diagnostic utility in isolation, the underlying processes they tap are likely to involve specific areas of weakness that are affected in ADHD smokers, facilitating the development and refinement of targeted interventions for this group.

ADHD-relevant treatment processes worthy of consideration in smoking cessation research Nicotine's effects on attention

There are several treatment processes to consider in the association between ADHD symptoms and persistent forms of tobacco use. First, it has been proposed that nicotine use may be negatively reinforced in individuals with high levels of ADHD symptoms by reducing the characteristic symptoms of ADHD, even among individuals with levels of ADHD symptoms that do not surpass diagnostic thresholds [5]. In smoking and non-smoking adults diagnosed with ADHD, nicotine administration enhances performance on attentional tasks [22].

ADHD & nicotine withdrawal

There is also growing evidence that individuals with ADHD symptoms experience more severe nicotine withdrawal symptoms during abstinence. For example, one laboratory study found that overnight abstinence caused more severe disruptions in cognitive inhibitory control (i.e., the ability to sustain attention and resist distracting stimuli) in adult smokers with ADHD as compared to non-ADHD smokers [23]. Given that inhibitory control is a pathognomonic marker of ADHD, these results may reflect the unmasking of ADHD-related deficits upon the discontinuation of nicotine. A recent populationbased study illustrated that smokers with higher levels of ADHD symptoms, particularly IN symptoms, were more likely to endorse experiencing a wide range of withdrawal symptoms (e.g., depressed mood, insomnia, irritability, anxiety, restlessness) during prior periods of smoking abstinence [24].

Etiological research on ADHD and withdrawal appears to generalize to clinical trials. Analyses of clinical trials suggest higher levels of overall withdrawal, negative affect, and craving are present in ADHD smokers making a cessation attempt [25]. These abstinence-induced changes could be interpreted either 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, smokers with higher levels of ADHD symptoms are likely to be more motivated to resume smoking following abstinence to suppress such undesirable nicotine withdrawal symptoms. The potential effects of nicotine withdrawal may be compounded by the characteristic ADHD deficits in inhibitory control, which could make it particularly difficult to inhibit strong impulses to smoke following a period of abstinence.

Scant existing empirical literature on ADHD in smoking cessation clinical trials

Smokers with ADHD report more failed quit attempts and lower rates of cessation than their non-diagnosed counterparts [6]. Furthermore, lower abstinence rates have been observed among smokers with predominantly HI than those with predominantly IN symptoms [26]. Consistent with the notion that ADHD symptoms play an important and complex role in cessation outcomes, there are some indications that methylphenidate, a common stimulant treatment for ADHD, may augment nicotine replacement therapy to improve cessation outcomes in heavily nicotine-dependent ADHD smokers with certain symptom profiles [15]. Similarly, a placebo-controlled study of a small group of adult smokers with ADHD (n = 15) found that ADHD medication improved laboratory measures of withdrawal symptoms (including withdrawal-induced cognitive disruptions)

after overnight abstinence and reduced salivary cotinine levels throughout a day in the natural environment [27]. According to ClinicalTrials.gov, there are at least two ongoing studies examining the efficacy of atomoxetine, a common non-stimulant treatment for ADHD, in substance use treatment for adolescents and adults with ADHD and comorbid substance use disorders, including nicotine dependence. Mindfulness-based treatment approaches that focus on behavioral techniques for coping with craving and resisting impulse control are also promising for this comorbid group and a handful of cessation trials incorporating mindfulness-based techniques are currently ongoing. However, outside of these very few studies, there is a dearth of research addressing ADHD in smoking cessation clinical trials.

Recommendations for clinical trials

Based on the information reviewed above, we urge scientists to consider assessing and possibly targeting ADHD in smoking cessation clinical trials in adults (and adolescents). It is common practice to measure depression in most smoking cessation clinical trials. We propose that ADHD might be as important to measure as depression and envision someday equally as commonplace in clinical trials. Preferably, we recommend incorporating a quantitative measure of ADHD symptom severity given the role of subclinical ADHD symptom variation in smoking cessation. We further suggest collecting ADHD data at the individual symptom dimension (IN and HI) level rather than at the broad syndrome level, which may overlook important heterogeneity across symptom subtypes that may differentially impact smoking cessation processes. At the very least, measuring ADHD might provide clinical insight about patient characteristics that predict smoking cessation treatment outcomes and perhaps even moderate treatment efficacy. Given that ADHD symptom alleviation may mediate smoking cessation treatment response, multi-time point ADHD assessment may be fruitful.

Finally, it may behoove the smoking cessation field to move towards developing and testing novel cessation treatments that offset the potential impact of ADHD on nicotine withdrawal and smoking relapse propensity. Given the widespread evidence implicating ADHD in smoking at the population level, treatment development efforts that consider targeting ADHD, at least in part, may help to raise rates of smoking cessation success more broadly and offset the massive public health burden associated with smoking.

Financial & competing interests disclosure

The authors are supported by the following grants: K23DA033302 (LC Bidwell) and K08DA025041 (AM Leventhal). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

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