Published in final edited form as:
Ann N Y Acad Sci. 2008 October ; 1141: 131–147. doi:10.1196/annals.1441.016.

ADHD and Smoking:

From Genes to Brain to Behavior

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) and tobacco smoking are among the most common and costly psychiatric and behavioral problems. The rates of co-occurrence of these two common problems are larger than expected by chance. Despite progress in identifying the neural and genetic substrates of each, the mechanisms underlying the high rates of comorbidity between ADHD and smoking remain largely unknown. We propose that ADHD and smoking involve dysregulation of dopaminergic and nicotinic-acetylcholinergic circuits and that these aberrations are likely to arise, at least in part, from genetic variations. This review describes an integrative model of the ADHD–smoking comorbidity, with an emphasis on shared neuropharmacological mechanisms. We first describe the prevalence of smoking among ADHD patients. We then describe how ADHD influences stages of smoking behavior (e.g., initiation, maintenance, and relapse). We review common potential genetic substrates of ADHD and smoking, focusing on genes that regulate monoaminergic neurotransmission. We review the behavioral and neuropharmacological bases of smoking and ADHD, focusing on the modulatory roles of nicotine on attention and behavioral control. Finally, we discuss the implications of this model for prevention and clinical outcomes.

Keywords

attention deficit hyperactivity disorder; nicotine dependence; smoking; nicotine; dopamine; impulsivity

Introduction

Cigarette smoking is the leading preventable cause of death and disability in the United States. Annually, smoking leads to more than 400,000 premature deaths in the United States and nearly 5 million deaths worldwide.[1] In the United States alone, $150 billion in annual costs are attributable to smoking-related illnesses and lost worker productivity.[2]

Several large-scale, epidemiologic studies have reported that individuals who have psychiatric disorders are significantly more likely to smoke than individuals from the general population.[3,4] The prevalence of smoking among individuals with a current psychiatric condition is nearly double that of individuals without current mental illness.[4,5] Although individuals who reported

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Conflicts of Interest

Dr. McClernon has received honoraria from Eli Lilly and research support from NIDA and the Atkins Foundation. Dr. Kollins has received research support or honoraria from the following sources: Shire Pharmaceuticals, Eli Lilly, Comentis, Psychogenics, Pfizer, Cephalon, New River Pharmaceuticals, NIDA, NIMH, NINDS, NIEHS, and EPA.

a psychiatric diagnosis in the past month make up approximately 30% of the U.S. population, they consume an estimated 44.3% of all cigarettes.[4] The number of co-occurring psychiatric disorders in an individual is also associated with higher levels of nicotine dependence and greater withdrawal severity.[4,6]

Most population- and clinic-based studies of smoking–psychiatric illness comorbidity have excluded attention-deficit/hyperactivity disorder (ADHD). This may be because ADHD is often considered a disorder of childhood and is thus not included as a psychiatric condition category when studying samples of adults. However, in the few studies in which the disorder has been examined, ADHD shows rates of comorbidity with cigarette smoking comparable to those of other psychiatric disorders (approximately 40%).[7] Moreover, recent evidence suggests that ADHD symptoms, even at levels below the threshold required to make a clinical diagnosis, are significantly associated with risk for smoking.[8] As such, a more thorough understanding of the relationship between ADHD and smoking has the potential to inform researchers and clinicians concerning mechanisms that underlie smoking risk in both ADHD-diagnosed and non-ADHD-diagnosed individuals. Despite the well-established associations between ADHD and smoking, comparatively little research has focused on this comorbidity.

In this review, we first provide a brief overview of the clinical characteristics of both ADHD and cigarette smoking. We describe the current knowledge about the prevalence of comorbid ADHD and smoking (ADHD–smoking) and how ADHD and related problems influence different stages of smoking (e.g., initiation, maintenance, and relapse). We then review the common potential molecular genetic substrates of ADHD and smoking, with an emphasis on genes that regulate monoaminergic neurotransmission. Following directly from this review of the potential genetic substrates of this comorbidity, we describe what is known about the behavioral and neuropharmacological bases of ADHD–smoking, focusing on the nicotinic-acetylcholine receptor and dopamine (DA) systems that influence cognitive functions. Based on this synthesis, we present a model of smoking risk in ADHD. We then discuss implications for the development of novel prevention and treatment efforts. Finally, we provide a synopsis of major review points along with questions for future research.

Attention-Deficit/Hyperactivity Disorder

ADHD is a genetically heritable, biologically driven disorder that involves developmentally inappropriate levels of inattention, hyperactivity, and impulsivity.[9] To meet the criteria for ADHD, an individual must exhibit at least six of nine inattention symptoms and/or six of nine hyperactive–impulsive symptoms to a degree that is beyond that expected for his or her developmental level. Symptoms must occur in multiple settings, must have been present and persistent since at least age 7, and must cause significant impairment in functioning in a major role (e.g., school, work, home life, and/or social settings). Finally, the symptoms must not be better accounted for by the presence of some other medical or psychiatric condition. ADHD affects approximately 5.3% of children and adolescents worldwide. It is estimated that 4.4% of adults in the United States meet the criteria for this disorder.[10,11] The impact of ADHD on the health care system and society is also staggering, costing tens of billions of dollars annually, in addition to personal and family suffering.[12]

As is the case with many, if not most psychiatric disorders, the prevalence of ADHD symptoms is distributed continuously in the population.[13] In other words, individuals may present with symptoms without meeting the full criteria for the disorder. Data from several population-based studies have found that ADHD symptoms canbeassociated with smoking behavior, whether or not ADHD diagnoses are present.[8,14] We further explore these and other studies in subsequent sections of this review.

Cigarette Smoking and Nicotine Dependence

Nicotine dependence is characterized by chronic and repetitive use of nicotine-containing products, withdrawal symptoms following cessation of use (e.g., depressed mood, irritability, and restlessness), and an inability to successfully quit despite knowledge that using such products are harmful to one's health.[9] Although a small number of individuals are able to maintain smoking behavior at low rates (i.e., fewer than five cigarettes per day), the majority of individuals who smoke do so at high rates.[15] However, not all smokers develop nicotine dependence: nearly 40% of individuals who smoke at least 10 cigarettes per day do not meet the criteria for nicotine dependence.[16]

Despite decreases in prevalence over the last three decades, more than 20% of the adult U.S. population smokes.[17] Experimentation with smoking typically begins during adolescent years. Regular, daily smoking typically starts soon thereafter.[18,19] Quitting attempts among adult U.S. smokers are frequent, but long-term unassisted quit rates are less than 5% at 6 months.[20–22] Moreover, pharmacologically and behaviorally supported smoking cessation treatments typically result in overall low success rates. For instance, nicotine replacement therapies result in long-term abstinence (6–12 months) rates of less than 20%[23,24] (see also Rose, this volume). Newer prescription medications, including the nicotinic partial agonist varenicline, have been shown to improve success rates.[25]

Overall Prevalence of ADHD–Smoking

Research using clinical samples indicates that individuals with ADHD smoke at rates that are significantly higher than those of the general population and/or nondiagnosed controls among both adults (41%–42% vs. 26% for ADHD and non-ADHD, respectively) and adolescents (19.0%–46% vs. 10%–24% for ADHD and non-ADHD, respectively).[7,26–28] A number of studies have reported that the co-occurrence of ADHD and substance use disorders in general can be accounted for almost completely by the presence of comorbid Conduct Disorder (CD).[29–31] However, investigators have shown that ADHD is a specific, independent risk factor for tobacco use in clinical and high-risk samples after controlling for comorbid CD.[28,32] Moreover, evidence suggests that specific problems with ADHD symptomsand related deficits in executive functioning significantly predict smoking, again even after controlling for conduct problems.[28,33,34]

In addition to research with clinical samples, several studies have found significant associations between ADHD symptoms and smoking behavior in community samples of adolescents.[14,35] In a population-based sample of over 15,000 young adults, a linear relationship was identified between the number of retrospectively self-reported ADHD symptoms and the lifetime risk of regular smoking.[8] This study also found a negative association between the number of ADHD symptoms and the age of onset of smoking. Among current smokers, it identified a positive association between the number of ADHD symptoms and number of cigarettes smoked per day. These findings are important because they raise the possibility that it is abnormalities in the underlying attentional and impulse control processes that engender smoking risk, as opposed to categorical diagnoses of ADHD per se.

Influence of ADHD or ADHD Symptoms on Stages of Smoking

Both ADHD and smoking are complex and heterogeneous phenotypes. Asa result, ADHD-related phenotypes might facilitate transition to and through different smoking stages (i.e., initiation, progression, and relapse) in myriad and complex ways. Independent evaluation of these associations can provide a more refined understanding of the mechanisms underlying the ADHD–smoking comorbidity and lead to more targeted prevention and treatment strategies.

Initiation of Smoking

Evidence suggests that individuals with ADHD start smoking at an earlier age.[26] In a longitudinal study of 140 children with ADHD and 120 nonpsychiatric controls, one study found that, at 4-year follow-up (mean age = 15.0 ± 3.6 years), the children with ADHD smoked at rates nearly twice as high as the control children (19% vs. 10%, respectively). Moreover, the mean age of onset of smoking for the ADHD group was 15.5 ± 2.0 years versus 17.4 ± 2.3 years for the controls. In addition, 75% of the ADHD smokers began smoking prior to age 16 versus only 27% of the non-ADHD smokers.[26] These findings are comparable to another retrospective study that found earlier ages of both first cigarette use and regular use for smokers with ADHD compared to those without.[36] In a nonclinical, population-based study of young adults, age of onset of regular smoking was found to be significantly associated with the number of retrospectively reported ADHD symptoms. Individuals reporting the highest levels of symptoms started smoking approximately 1.25 years earlier than individuals reporting the lowest levels of symptoms (16.67–16.73 years vs. 15.44–15.48 years).[8]

Progression to Regular Smoking

ADHD symptoms have also been shown to influence the trajectory of smoking behavior from initial use to regular use and dependence. One study found that a lifetime diagnosis of ADHD was a significant predictor of progression from initiation of smoking to daily use.[37] A more recent study evaluated the relative contributions of inattentive versus hyperactive–impulsive ADHD symptoms on the progression of smoking behavior in a population-based study of young adults.[38] When compared with individuals reporting low levels of ADHD symptoms, those reporting high levels of hyperactive–impulsive ADHD symptoms were 1.9 times as likely to progress from no smoking at Wave 1 (mean age = 15.7 years) to regular smoking at Wave 3 (22.96 years). They were 3.25 times as likely to progress from experimentation at Wave 1 to regular smoking at Wave 3. This study also found that high levels of inattentive ADHD symptoms did not predict smoking progression.[38]

Severity of Regular Smoking

Two studies of population-based samples have shown that levels of ADHD symptoms predict levels of nicotine use and dependence. Among current regular smokers, self-reported numbers of both hyperactive–impulsive and inattentive ADHD symptoms significantly predicted the number of cigarettes smoked per day.[8] A second study conducted using the same sample found that both ADHD symptom domains were associated with levels of nicotine dependence, as measured by the Fagerstro¨m Test of Nicotine Dependence, among current smokers.[38] These studies stand in contrast to two studies that have found no differences in numbers of cigarettes smoked or levels of nicotine dependence in adult smokers with ADHD compared with non-ADHD control groups.[36,39] The differences across these studies may well relate to the sampling strategies used. The latter two studies were conducted with samples selected for both ADHD diagnosis and smoking status, whereas the former studies were population-based samples, the inclusion criteria for which did not depend on either of these factors. These differences highlight the importance of distinguishing between ADHD diagnoses and continuously measured ADHD symptoms.

Smoking Cessation and Relapse

Evidence suggests that ADHD and non-ADHD individuals may differ in their rates of quitting smoking and their ability to maintain smoking abstinence. The percentage of ever-smokers who became ex-smokers is lower among adults with ADHD (29%) compared with the general population (48.5%).[7] Individuals with ADHD may thus have greater difficulty quitting. Histories of childhood ADHD can predict worse smoking cessation outcomes, even after controlling for demographic, baseline smoking variables and depression symptoms.[40]

One possible explanation for these differences in quit rates and cessation outcomes is that smokers with ADHD can differ from non-ADHD smokers in the severity of withdrawal symptoms. Smokers with psychiatric comorbidities (other than ADHD) exhibit greater smoking withdrawal severity than smokers without psychiatric comorbidities.[4] Conceivably, this observation might help to explain why psychiatrically ill patients smoke at such high rates.[41] Two studies have also directly compared ADHD and non-ADHD smokers' withdrawal symptom severities. In one study, retrospective smoking withdrawal symptoms were evaluated in adult smokers with current ADHD, adult smokers with a history of childhood but not current ADHD, and adult smokers who report neither childhood nor current ADHD. Individuals in the ADHD groups reported experiencing greater irritability and difficulty concentrating during quit attempts compared to smokers without a history of ADHD or current ADHD.[36] In another study, ADHD symptoms were measured prospectively in ADHD and non-ADHD smokers in a laboratory setting.[39] No significant differences in self-reported withdrawal symptom severity were observed between the two groups following a 12-h abstinence. However, following abstinence, ADHD smokers exhibited a greater worsening of performance on a Continuous Performance Test (CPT), with greater numbers of errors of commissions and greater reaction time variability than did non-ADHD smokers. Collectively, these findings suggest that ADHD smokers may be differentially sensitive to the effects of smoking abstinence. This differential sensitivity might encompass effects on both withdrawal symptomatology and changes in cognitive function. These changes may also lead to increased risk for relapse in individuals with ADHD or high levels of ADHD symptoms that accompany quit attempts.

Section Summary

ADHD phenotypes, defined either as DSM-based clinical diagnoses, or as continuously distributed symptom counts, are significantly associated with all stages of smoking, including smoking initiation, progression to regular use, level of smoking and nicotine dependence, and withdrawal and relapse. Although these studies demonstrate important links between ADHD and various aspects of smoking behavior as it develops over time, they have largely been retrospective in nature, thus limiting our ability to draw conclusions about underlying mechanisms or causality. Studies that are both prospective and longitudinal in nature and studies that track the trajectory of ADHD symptoms or diagnosis and smoking outcomes are needed to further understanding of the mechanisms for this ADHD–smoking comorbidity.

Common Genetic Substrates of ADHD and Tobacco Smoking

Both ADHD and smoking are highly heritable; genetic factors account for 60%–80% and 56% of the two phenotypes, respectively.[42,43] Candidate gene studies have identified a number of similar genetic markers associated with both ADHD and smoking phenotypes, suggesting that several common neurobiological mechanisms may give rise to this comorbidity.[44–47]

Molecular Genetics of ADHD and Treatment Response

A recent meta-analytic review identified variants in seven genes that have shown statistically significant evidence of association with ADHD on the basis of pooled odds ratios across at least three studies.[42] Four of these genes are involved in DA neurotransmission and metabolism: the dopamine D4 and D5 receptor genes (DRD4, DRD5), the dopamine transporter gene (DAT1), and the dopamine beta hydroxylase gene (DBH). Two additional genes are involved in serotonin neurotransmission: the serotonin HTR1B gene and the serotonin transporter gene (5-HTT). Finally, considerable evidence suggests that the synaptosomal-association protein 25 gene, which is related to exocytotic neurotransmitter release, is associated with ADHD. Variants of this gene result in significant hyperactivity in mouse models.

Evidence also suggests that the efficacy of stimulant drugs like methylphenidate in the treatment of ADHD is moderated, in part, by genetic factors.[48] For example, variations of both the DRD4 and DAT1 genes have been shown to influence the efficacy of methylphenidate in trials with pediatric populations.[49–51] In addition, some evidence suggests that genetic variants are associated with the potential for side effects associated with stimulant treatment in children diagnosed with ADHD.[52]

To date, six genome-wide linkage-based studies of ADHD have been published, representing four samples.[53] Considered separately, three of the groups have reported LOD scores indicating definite or suggestive linkage on three different chromosomes (16p13, 15q, and 11q22).[54–56] The only chromosomal region that has been shown to have a LOD score greater than 1 in more than one of the separate studies was located at 5p13.[55,57,58] Interestingly, this region is also close to the location for the candidate gene DAT1; variation in the DAT1 gene might conceivably contribute to the linkage findings at the 5p13 locus. A number of large-scale efforts currently under way throughout the world will greatly increase the power to detect meaningful linkage in larger samples.[59]

Smoking

Candidate gene studies of smoking behavior have focused on many of the same monoamine regulating genes as have ADHD studies. Variants of the DRD4, DAT, and DBH genes, as well as the HTR1B and 5-HTT genes have been shown to be associated with higher levels of smoking behavior in a range of populations.[60–68] In addition, a haplotype of the DRD5 gene appears to be protective against smoking phenotypes.[69] In a meta-analytic review of candidate genes associated with multiple smoking phenotypes, modest yet significant associations were observed between DRD2 and both smoking initiation and consumption and between 5HTT-LPR and smoking cessation outcomes.[46] The seven-repeat (or longer) allele of the DRD4 VNTR has also been associated with behavioral and brain responses to smoking-related cues, suggesting that the D4 receptor system potentially plays a critical role in cue-provoked smoking and relapse.[61,70]

More recently, greater attention has been paid to candidate genes involved in nicotinic receptor system activity.[71,72] SNPs of the nicotinic receptor alpha4 subunit gene (CHRNA4) have been associated with the a range of smoking phenotypes.[72,73] SNPs of the beta2 subunit gene (CHRNB2) have been shown to be associated with initial response to smoking but not with nicotine dependence[73,74]

As with ADHD, a growing number of genome-wide linkage studies have been conducted in a search for the genetic bases for smoking phenotypes. To date, regions on chromosomes 9, 10, 11, and 17 have been most reliably replicated.[75] Genes within these regions regulate a wide range of functions, some with obvious connections to neurotransmitter function (e.g., the γ-aminobutyric acid receptor 2 on chromosome 9).

Recent data also suggest that genetic factors account for approximately half of the variability in relapse following a quit attempt.[41] Pharmacogenetic trials have provided preliminary evidence that many of the same genes associated with nicotine dependence are modestly related to smoking cessation outcomes.[76] For instance, the *Taq* 1 A2/A2 allele at the DRD2/ANKK1 gene locus was associated with better short-term nicotine replacement therapy outcomes, but better longer-term outcomes among female smokers only.[77] In addition, the *Taq* A1 allele of the DRD2/ANKK1 locus was associated with less responsiveness to bupropion.[78]

Overlap in Genetic Substrates of ADHD and Smoking

Clearly, the genetic substrates of ADHD and smoking behavior overlap considerably, with a number of candidate genes, most notably DRD4 and DAT, exhibiting associations with both phenotypes.[42,46] In addition, several studies have examined the relationship among genes, smoking, and ADHD. A study that examined interactions between gene × ADHD symptoms found effects for both DRD2 and, among females, MAO-A.[79] In that study, carriers of the DRD2/ANKK1 *Taq*1 A2/A2 allele with six or more hyperactivity–impulsivity symptoms were almost twice as likely to have a history of smoking as individuals carrying the A1 allele. Another study observed significant interactive effects of *in utero* exposure to smoking and either DAT1 or DRD4 polymorphisms in predicting combined type ADHD.[80] This same group observed a similar interaction between *in utero* smoke exposure and an exon 5 polymorphism of the CHRNA4 gene in predicting combined type ADHD.[81]

Genes regulating nicotinic receptor functioning are another group of potential targets that might allow us to identify genetic overlaps between ADHD and smoking. As noted above, a number of studies have found that variation in these genes can relate to smoking behavior. In addition, at least five studies have examined relations between the CHRNA4 gene and ADHD. However, findings have been mixed. One study found a significant association between variation in this gene and a quantitative phenotype of ADHD, whereas another study failed to identify any significant association between the gene and ADHD.[82,83] Three additional studies have reported nominally significant associations between the CHRNA4 gene and ADHD phenotypes.[84–86] No association was observed between ADHD and CHRNA7 microsatellite markers.[87] Although the interactive effects of nicotinic receptor genes and psychiatric symptomatology has been studied in the context of schizophrenia, no similar studies have been conducted for ADHD. This provides an obvious area for additional research.[88]

Section Summary

The literature presented here suggests a great deal of commonality in the genetic substrates underlying both ADHD and smoking. Most of this overlap involves genes that regulate monoaminergic transmission, with a particular focus on DA system genes that include DRD4 and DAT. Evidence also suggests that nicotinic receptor genes may be associated with both smoking and ADHD. The few studies that have examined relations among genes, smoking, and ADHD have shown that (1) ADHD symptoms interact with genes to increase smoking risk and (2) *in utero* smoke exposure may interact with genes to increase the odds of ADHD. These studies highlight the need for additional work to more precisely characterize the pathways from genetic variation to both smoking and ADHD-related phenotypes. Additionally, although genome-wide linkage studies are available for both ADHD and smoking phenotypes, these studies have not shown common areas of linkage. Future genome-wide association analyses of samples that include both ADHD and smoking status as phenotypes may be required to determine whether specific chromosomal regions confer risk for both conditions. Pharmacogenetic studies have identified genetic markers for ADHD and smoking cessation treatment response separately. Future research might seek to identify whether smoking status interacts with genotype to predict ADHD treatment outcomes or, conversely, whether ADHD status interacts with genotype to predict smoking cessation outcomes.

Neuropharmacological and Behavioral Factors in ADHD–Smoking

Despite the relative lack of direct work concerning the mechanisms responsible for increased risks of smoking in individuals with ADHD, several lines of research provide convergent evidence that both neurobiological and behavioral factors may contribute to the high rates of smoking in these individuals.

Neurobiological and Neuropharmacological Factors

From a neuropharmacological perspective, ADHD is hypothesized to be the result of an aberrant striatal dopaminergic system that results in disrupted dopaminergic transmission in corticostriatal circuits. These disruptions, in turn, give rise to the characteristic deficits in executive functioning observed in ADHD patients.[89,90] This altered DA hypothesis is supported by studies showing differences in DAT density in relevant striatal areas in ADHD patients compared with controls.[91–99] Although these studies have reported discrepant findings with respect to the direction of DAT density change (i.e., some report higher levels, and some report lower levels in ADHD), collectively they suggest associations of DAT density and its consequent effects on DA neurotransmission with the clinical condition of ADHD.

Drawing on both preclinical and clinical studies, one possible implication of altered DA functioning is that ADHD patients exhibit lower DA tone as a result of lower-than-normal activation of presynaptic DA autoreceptors, resulting in exaggerated phasic DA responses to salient stimuli.[89] Nicotine has been shown to stimulate DA release in the striatum of both animals and human smokers.[100,101] We therefore propose that nicotine-stimulated phasic DA release may be more rewarding in individuals with ADHD compared with non-ADHD individuals. This enhanced reward salience would lead to higher levels of nicotine reinforcement after first use, thus facilitating the transition to continued use in this population. In other words, ADHD patients might experience higher initial rewarding effects of nicotine than those without ADHD because of fundamental differences in DA function.

Behavioral Mechanisms: Attention, Behavior Inhibition, and ADHD Symptoms

At a behavioral level of analysis, several different processes could account for the higher rates of smoking among individuals with ADHD or with high levels of ADHD symptoms. It has been proposed that nicotine use may be negatively reinforced in some individuals by reducing the characteristic symptoms of ADHD, even if those symptoms do not reach clinical thresholds.[35] These processes include increased withdrawal severity (reviewed above) and the direct effects of nicotine on attention, behavioral inhibition, and ADHD symptoms.

Attention—Nicotine has been shown to improve performance on a range of attentional tasks in both human and nonhuman subjects.[102–104] In human studies, nicotine administration has resulted in improved performance on attentional tasks in regular smokers and in nonsmokers.[105,106] For example, one study found that smoking improved abstinence-related cognitive disruptions in smokers with schizophrenia.[107] Nicotine administration has also resulted in enhanced attentional performance in smoking and nonsmoking adults diagnosed with ADHD. Specifically, transdermal nicotine (7 mg or 21 mg administered to nonsmokers and smokers, respectively) decreased both reaction time and reaction time variability on a CPT.[108]

Behavioral Inhibition—Behavioral inhibition is a broad construct relating to an individual's ability to withhold an inappropriate or maladaptive response. Deficits in behavioral inhibition are theorized to be central distinguishing features of individuals with ADHD versus nondiagnosed individuals.[109] The effects of nicotine on behavioral inhibition may be more subtle than those observed for attention. Studies of nonsmokers suggest that nicotine only marginally improves behavioral inhibition as measured by errors of commission on a CPT task.[105,110] Among nonsmoking adolescents and young individuals with ADHD, nicotine enhanced one measure of response inhibition, stop signal reaction time, but had no effect on a CPT measure of response inhibition in adult nonsmokers.[111–113]

ADHD Symptoms—Nicotine has also demonstrated clinical efficacy for individuals with ADHD. One study in ADHD patients showed that transdermal nicotine (7 mg/day) improved clinical global impressions of ADHD symptomatology while it increased self-ratings of

positive affect.[108] Two other studies have shown that novel nicotinic agonists display efficacy in reducing both inattentive and hyperactive–impulsive symptoms in adults with ADHD.[114, 115] Efficacy in these latter studies was not altered by current or lifetime smoking status.

The above evidence indicates that nicotine and nicotinic agonists improve symptoms of ADHD, lending support to "self-medication" hypotheses of smoking among individuals with ADHD. Several caveats to this conceptualization are worth mentioning, however. First, studies demonstrating beneficial effects of nicotine on cognition in smokers cannot distinguish between absolute effects of nicotine versus their benefits in alleviating withdrawal. Further, most of the small number of human studies that show beneficial effects of nicotine on attention, impulsivity, and ADHD symptoms in nonsmokers had small sample sizes and produced effects of relatively small magnitude. Thus, although a small but growing body of evidence points to negatively reinforced reduction in ADHD symptoms by smoking, additional research is needed to accurately evaluate both the magnitude and scope of this phenomenon.

An Integrated Model of ADHD–Smoking Comorbidity

Despite the considerable amount of descriptive work that has characterized associations between ADHD and smoking, relatively little research has been conducted to elucidate the mechanisms underlying this common comorbidity. In an effort to consolidate what is known and to also generate hypotheses to be tested in future research, we have developed a multifactor model of nicotine use and dependence in ADHD (see Fig. 1). Relevant aspects of this model are reviewed below.

Individuals with ADHD exhibit psychological and biological vulnerabilities that influence both the likelihood that they might experiment with nicotine and the reinforcing effects of initial use. With respect to risk for experimentation, individuals with ADHD are more impulsive, score higher on measures of novelty seeking, and have more problematic peer interactions than nondiagnosed individuals. Each of these factors is considered an independent risk factor for smoking.[116–123] This overlap in psychological and social risk is likely to be driven, in part, by common genetic and neurobiological factors.

From a neuropharmacological perspective, ADHD is hypothesized to result from aberrant striatal dopaminergic systems that result in disrupted dopaminergic transmission in corticostriatal circuits. These disruptions, in turn, can give rise to the characteristic deficits in executive functioning observed in ADHD patients. They have important implications for several aspects of smoking behavior as reviewed above. First, individuals with ADHD are hypothesized to have lower tonic DA tone which may amplify the phasic DA response stimulated by nicotine; this, in turn, may enhance the reward salience of smoking in this population. Second, deficits in attentional and inhibitory control functions are reduced by nicotine, which negatively reinforces continued use. Third, upon quitting smoking, individuals with ADHD experience greater withdrawal symptom severity and greater disruption of inhibitory control, increasing the likelihood of relapse. Finally, higher baseline levels of impulsivity and greater sensitivity to salient rewardrelated cues may confound efforts to maintain smoking abstinence.

A number of family and social variables represented in this model, which have not been thoroughly evaluated in this review, represent important moderators or mediators of the association between ADHD and smoking. For example, it is well established that deviant peer relations and parenting styles are associated with both ADHD and smoking.[124–128] Delineating more precisely the manner in which these and related constructs interact should help us to better understand the developmental trajectory of smoking behavior in individuals with ADHD and/or with high levels of ADHD symptoms.

Prevention and Treatment Implications

The above model highlights a number of compelling research questions that could help us to elucidate mechanisms underlying the prevalent comorbidity of ADHD and smoking. A critical aspect of any model of maladaptive behavior, however, is the extent to which it can inform clinical and community-based interventions.

The foregoing review and proposed framework suggest several applications for preventing and reducing smoking and nicotine dependence in individuals who are vulnerable as a result of ADHD and related risk factors. As reviewed above, a number of studies have shown that both a diagnosis of ADHD and ADHD symptomatology (independent of clinical diagnosis) are associated with lifetime risk of regular smoking, higher levels of smoking, and earlier initiation of smoking. These findings suggest that young people with ADHD and/or those who manifest a number of ADHD symptoms might be preferentially targeted for prevention efforts. A sizable literature exists on community and school-based smoking prevention programs.[129,130] It is not known, however, whether individuals at risk for smoking as a result of ADHD-related problems would benefit from existing prevention programs, or if they would require novel alternative approaches. Several of the more successful current prevention programs focus on peer and family influences.[129,130] It is well established, however, that individuals with ADHD have significant deficits in peer relationships.[131] Further, coping skills and parent–child communication have been shown to mediate the association between ADHD and smoking outcomes.[132] As such, individuals with ADHD or related symptomatology may benefit from prevention programs that specifically target these important mediating processes.

Our review and proposed model also form the basis for several innovative approaches to treating individuals with ADHD and related problems who have initiated regular smoking. It has been shown that individuals with ADHD have a harder time quitting smoking and show more significant signs and symptoms of smoking withdrawal.[7,36,39] Based on these findings and much of the other literature reviewed, it could be argued that individuals with ADHD and related problems smoke, in part, to reduce the requisite symptoms of inattention, hyperactivity, and impulsivity. Based on this conceptualization, treatment strategies that improve these deficits prior to and during a quit attempt may be successful in facilitating smoking cessation among individuals with ADHD. This approach is currently being evaluated in a large clinical trial funded by the National Institute on Drug Abuse. This study will evaluate whether a sustained release formulation of methylphenidate (Concerta®), relative to placebo, increases the effectiveness of a standard smoking treatment (i.e., a nicotine patch and individual smoking cessation counseling) in obtaining prolonged abstinence for adult smokers with ADHD (http://www.clinicaltrials.gov/ct/show/NCT00253747?order=1). Similarly, novel pharmacological interventions that target either cholinergic or dopaminergic systems have shown some promise in treating both smoking and ADHD. For example, bupropion has shown efficacy in treating adults with ADHD and has also been approved by the Food and Drug Administration as an aid to smoking cessation.[133–135] Novel cholinergic agents have also shown promise in treating adults with ADHD.[114,115] Whether these agents would work for treating comorbid ADHD–smoking is largely unknown, although one open-label pilot study with adolescents reported positive results.[136]

Based on the conceptualization reported here for how ADHD and smoking behavior might be related, it stands to reason that nonpharmacological approaches to treating ADHD might also be useful in facilitating smoking cessation. Emerging work shows promise for the use of cognitive-behavioral treatment of adults with ADHD. It would be important to evaluate whether these treatment approaches would serve as useful adjuncts to smoking cessation in those with ADHD.[137]

Conclusions

Tobacco use among individuals diagnosed with ADHD or among individuals with elevated ADHD symptoms represents a significant public health problem. Significant progress has been made in the last 5–10 years to understand the prevalence and developmental trajectory of ADHD and smoking. More recent work has begun to focus on the genetic and neural underpinnings of these comorbid problems. Significantly more work is necessary before a full picture of the mechanisms underlying this association is available. As these underlying mechanisms are elucidated more fully, progress can be made in developing novel prevention and treatment strategies for reducing the harm associated with tobacco smoking in this population. Below we provide a synopsis of the most salient findings of the current review along with questions for future research.

1. A disproportionately large number of individuals with ADHD smoke. Moreover, ADHD symptoms, even in the absence of a clinical diagnosis, represent a risk factor for smoking. *Research questions: Are the processes associated with ADHD (i.e., attention and inhibitory control) also associated with the comorbidity of smoking and other psychiatric disorders (e.g., schizophrenia and depression)? Are there variables (e.g., gender and / or race or ethnicity) that moderate the relationship between ADHD and smoking*?

2. Individuals with ADHD or elevated ADHD symptoms retrospectively report initiation of smoking at an earlier age and are more likely to progress to regular smoking. Hyperactive–impulsive symptoms appear to be a more important factor in smoking progression than inattentive symptoms. *Research questions: Do individuals with ADHD have initial reactions to their first cigarette that differ in type or magnitude from the reactions of individuals who do not have ADHD? What environmental, social, or psychological factors mediate the relationship between ADHD and earlier smoking*?

3. The number of ADHD symptoms, independent of clinical diagnosis, is associated with greater cigarette consumption and higher levels of nicotine dependence. *Research questions: Do ADHD and non-ADHD smokers differ in terms of smoking reinforcement? What factors (e.g., stress or cognitive demands) modulate smoking behavior among individuals with ADHD*?

4. Individuals with ADHD retrospectively report greater difficulty quitting smoking and exhibit greater problems with inhibitory control following quitting. A childhood history of ADHD is predictive of worse smoking cessation outcomes. *Research questions: How do the trajectories of nicotine withdrawal symptoms differ between ADHD and non-ADHD smokers? What are the immediate antecedents to smoking in ADHD smokers during both* ad lib *smoking and lapse or relapse? Do these immediate antecedents differ from those of non-ADHD smokers? What are the neurobiological correlates of differences between ADHD and non-ADHD smokers in withdrawal response*?

5. Variants in genes that regulate monoaminergic transmission are associated with both ADHD and smoking. *Research questions: Will genome-wide studies identify chromosomal loci common to ADHD and smoking? How do genetic differences lead to differences in brain function that increase risk of smoking among individuals with ADHD? Are there epigenetic processes that contribute to the development of smoking in individuals with ADHD*?

6. ADHD is hypothesized to be the result of an aberrant striatal dopaminergic system which, in turn, gives rise to deficits in executive functioning. Disruption of this system increases the reward value of self-administered nicotine, results in negative

reinforcement of attentional and inhibitory control deficits by smoking, worsens nicotine withdrawal, and promotes relapse by increasing baseline levels of impulsivity and reward sensitivity. Drugs that are used to treat both ADHD and smoking cessation exert direct and indirect influence on dopaminergic pathways. *Research questions: Do nonsmokers with and without ADHD differ in their brain response to nicotine? Which brain regions mediate these differences? Do brain correlates of nicotine withdrawal differ between ADHD and non-ADHD smokers*?

7. Prevention of smoking among individuals at risk because of ADHD symptomatology will require identification of youths with these risk factors and novel strategies aimed at improving social (family and peer) skills. *Research question: Can interventions that target children based on ADHD symptoms or diagnosis reduce their risk of becoming smokers*?

8. Smoking cessation interventions among individuals with ADHD might attempt to treat ADHD symptoms prior to quitting smoking. Pharmacological interventions will probably focus on medications efficacious in treating ADHD, smoking, or both. *Research questions: Does pretreatment with DA agonists (e.g., methylphenidate or amphetamine) facilitate smoking cessation in individuals with ADHD? Would adjunct treatment with DA agonists and either nicotine (i.e., transdermal) or other cholinergic agents increase the probability of cessation in individuals with ADHD*?

Acknowledgments

This research was supported by NIDA grants K23DA017261 (McClernon) and R21DA-020806 (Kollins). Please contact me (and cc my coauthor, Dr. Scott Kollins) if I can provide any additional information.

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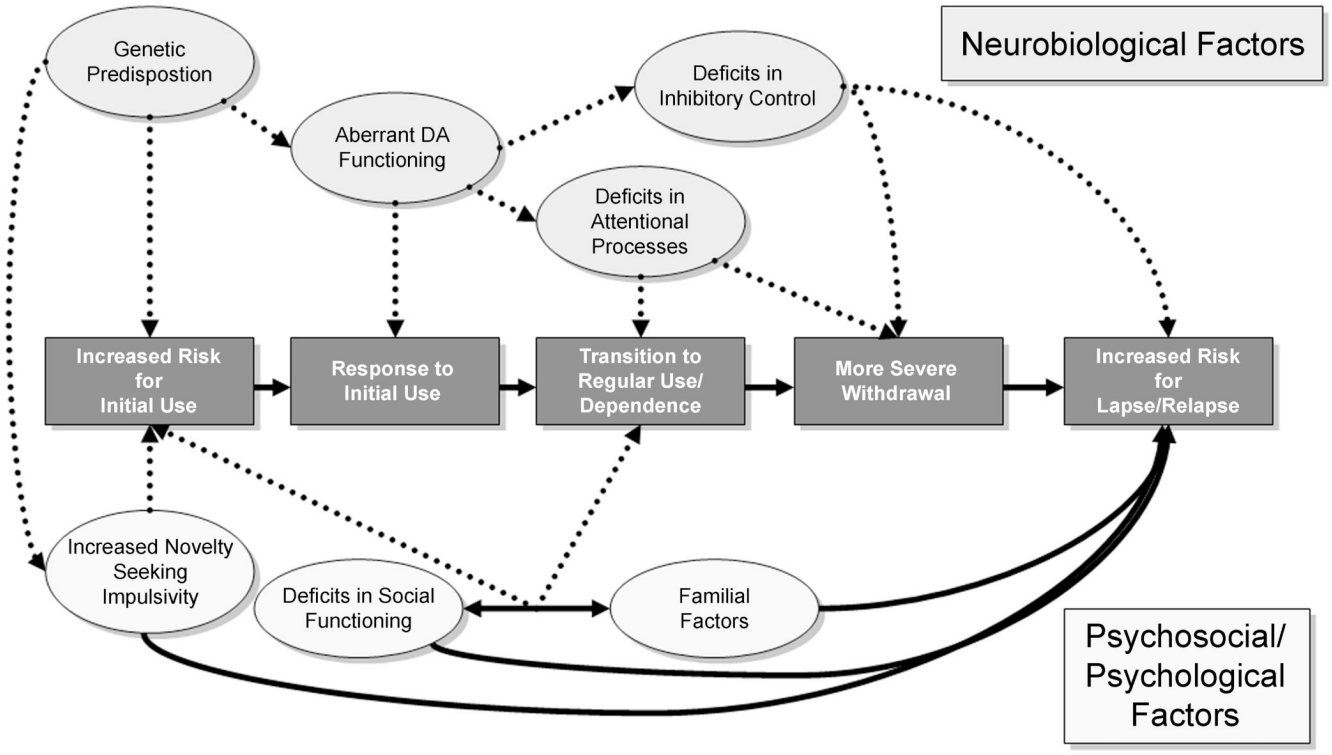

Figure 1.
Model of risk for nicotine use and dependence in ADHD. Neurobiological factors (*top*) combine with psychological and psychosocial factors (*bottom*) to increase risk for various stages of nicotine use and dependence. Areas of the model in the shaded box will be the focus of the application.