Stimulant Treatment of ADHD and Cigarette Smoking: A Meta-Analysis

abstract

BACKGROUND AND OBJECTIVE: Individuals with attention-deficit/hyperactivity disorder (ADHD) have a significantly higher risk of cigarette smoking. The nature of the relationship between smoking and psychostimulant medications commonly used to treat ADHD is controversial. Our objective was to examine the relationship between stimulant treatment of ADHD and cigarette smoking by using meta-analysis, and to identify study and sample characteristics that moderate this relationship.

METHODS: Literature searches on PubMed and PsycInfo databases identified published studies for inclusion. Included studies compared cigarette smoking outcomes for stimulant-treated and untreated ADHD individuals. Seventeen studies met inclusion criteria, and 14 (total $n = 2360$) contained sufficient statistical information for inclusion in the meta-analysis. Two authors extracted odds ratios or frequencies of smokers in the treatment or nontreatment groups, and coded study characteristics including sample source, percentage of male participants, follow-up length, treatment consistency, type of smoking measure, prospective study, and controlling for comorbidities.

RESULTS: Meta-analysis revealed a significant association between stimulant treatment and lower smoking rates. Meta-regression indicated that effect sizes were larger for studies that used clinical samples, included more women, measured smoking in adolescence rather than adulthood, conceptualized stimulant treatment as consistent over time, and accounted for comorbid conduct disorder.

CONCLUSIONS: Nearly all studies were naturalistic, precluding causal inferences. Available data were insufficient to examine additional influences of patient demographics, treatment effectiveness, or other comorbidities. Consistent stimulant treatment of ADHD may reduce smoking risk; the effect was larger in samples with more severe psychopathology. Implications for further research, treatment of ADHD, and smoking prevention are discussed. *Pediatrics* 2014;133:1070–1080

AUTHORS: Erin N. Schoenfelder, PhD,^a Stephen V. Faraone, PhD,^b and Scott H. Kollins, PhD^a

^a*Department of Psychiatry and Behavioral Sciences, School of Medicine, Duke University, Durham, North Carolina; and*
^b*Departments of Psychiatry and of Neuroscience and Physiology, State University of New York Upstate Medical University, Syracuse, New York*

KEY WORDS

ADHD, psychostimulant medication, cigarette smoking, meta-analysis

ABBREVIATIONS

ADHD—attention-deficit/hyperactivity disorder

CD—conduct disorder

CI—confidence interval

DSM-IV—*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*

HR—hazard ratio

ND—nicotine dependence

OR—odds ratio

Dr Schoenfelder co-conceptualized and designed the study, extracted data, conducted analyses, and drafted the initial manuscript; Dr Faraone consulted on the analytical strategy, and reviewed and revised the manuscript; Dr Kollins co-conceptualized and designed the study, participated in data extraction, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders^{1–3} and confers risk for a variety of functional impairments into adulthood.⁴ One of the most costly and well-documented of these risks is higher rates of cigarette smoking.^{5,6} Youth with ADHD are 2 to 3 times more likely to smoke cigarettes than their peers without ADHD.^{7–12} They also begin smoking earlier^{7,13} and progress more quickly to regular use and dependence.⁸ ADHD youth smokers are also at higher risk for drug and alcohol use disorders than youth with ADHD who do not smoke.^{14,15} The association between ADHD and smoking persists across development, with 40% of adults with ADHD smoking regularly,¹⁶ compared with ~19% of the general population.¹⁷ Furthermore, adults with ADHD have lower rates of success with smoking cessation than adults without ADHD.^{8,18} Given the enormous burden smoking places on public health,¹⁹ it is critical to identify factors that influence the development of nicotine use in youth with ADHD to inform prevention and treatment efforts.

Convergent evidence suggests that stimulant medication (ie, d-amphetamine, methylphenidate), which is a front-line treatment of ADHD, may influence smoking-related outcomes. Nicotine operates on the same dopaminergic pathways as these medications^{20,21} and, like stimulants, improves neurocognitive processes that are disrupted in ADHD.^{22,23} Nicotine enhances attention in both ADHD and non-ADHD individuals, and improves clinical functioning in patients with ADHD.²⁴ There is also evidence for the efficacy of nicotinic agonists and partial agonists as monotherapy for adults with ADHD,^{25,26} though these effects have not been consistently replicated.^{27–29} Thus, it has been suggested that individuals with ADHD “self-medicate” their attentional deficits with nicotine delivered via cigarette smoking.^{30–33}

The evidence on how stimulant drugs influence smoking behavior is mixed. Several laboratory studies, including 1 with ADHD smokers, have revealed that methylphenidate or amphetamine increase cigarette smoking.^{34–39} In contrast, however, a recent study revealed no effect of methylphenidate on choices of cigarette puffs versus money for ADHD and non-ADHD adults.⁴⁰ Randomized clinical trials of stimulants to aid cessation among ADHD smokers have revealed no evidence that either methylphenidate or amphetamine products are more effective than placebo for facilitating smoking abstinence.^{41,42} However, in contrast to some laboratory studies, both stimulant and placebo-treated individuals in these studies reduced the number of cigarettes smoked daily,^{42,43} and 1 open label study revealed that methylphenidate treatment decreased smoking to below the population rate.⁴⁴

Longitudinal studies that have examined smoking outcomes in stimulant-treated ADHD youth provide a more robust approach to evaluate the relationship between stimulant treatment and smoking outcomes. A recent meta-analysis⁴⁵ including smoking outcome data from 5 longitudinal studies revealed no overall effect of stimulant treatment on “ever trying” cigarettes or on a subsequent *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) diagnosis of nicotine dependence (ND). However, additional measures of smoking may be of interest in conceptualizing smoking outcomes for adolescents, because the majority of adolescent smokers do not meet full criteria for ND,^{46,47} which may take several years to develop after smoking initiation.⁴⁷ Frequency of smoking is found to be a better predictor of the progression to regular smoking than ND for adolescents who are newer to smoking.⁴⁸ Defining smoking more broadly may therefore increase sensi-

tivity to detect differences between treated and untreated youth.

The current study is a meta-analysis of more than a dozen longitudinal studies. We sought to ascertain the nature and magnitude of the association between stimulant treatment and smoking by using a large and diverse sample. The study advances knowledge from previous reviews and meta-analyses on the topic in several important ways. First, we included a broader range of smoking measures in addition to ND, which provides a substantially larger sample. Second, we examined methodological discrepancies across studies that may help explain differences in findings across studies, specifically in regard to sample characteristics (age, type of sample), definition of stimulant treatment, smoking outcome measure, and consideration of comorbid externalizing problems. Our goal was to identify factors that may contribute to smoking risk for stimulant-treated youth, which would therefore have implications for effective prevention and treatment practices. A thorough examination of the association between stimulant treatment and smoking serves to inform efforts to prevent smoking in ADHD youth, who have not previously been targeted for smoking prevention efforts despite the well-known ADHD-smoking comorbidity.

METHODS

Search Procedure

Studies were identified by using searches in PubMed and PsycInfo databases including the following: [ADHD, ADD, attention deficit, attention deficit/hyperactivity disorder, hyperactive, hyperkinetic] AND [stimulant, pharmacotherapy, psychostimulant, medication, methylphenidate, amphetamine, treatment] AND [substances, cigarette, nicotine, smoking, tobacco]. We also used the ancestry approach whereby we examined the reference sections of relevant studies to find other

articles that met criteria. The last search was conducted in July 2013.

Eligibility Criteria

Studies selected for the current meta-analysis met the following criteria:

Participants

Studies included a sample identified as having ADHD or clinically elevated ADHD symptoms. Diagnosis was established through DSM-based diagnostic evaluation or family-reported previous diagnosis of ADHD; standardized ADHD rating scales were used to establish clinical elevations. We excluded samples recruited due to current smoking (ie, smoking cessation trial).

Study Design

We included randomized or non-randomized treatment studies, as well as prospective or retrospective naturalistic studies.

Intervention

Studies compared at least 2 treatment groups, with at least 1 group receiving psychostimulant treatment of ADHD.

Outcome

Any measure of cigarette smoking was sufficient for inclusion in the overall review. For inclusion in the meta-analysis, studies had to include a binary measure of regular smoking.

Publication

Peer-reviewed journal articles or book chapters published in English between 1980 and July 2013 were included.

Data

For inclusion in the meta-analysis, studies must have revealed sufficient information to ascertain the number of smokers in the treated and comparison groups, or provided an odds ratio (OR) or hazard ratio (HR) comparing smoking prevalence across treatment groups. Studies

were excluded for the following reasons: insufficient data available/lack of outcome measure consistent with regular smoking; no ADHD sample; smoking cessation trial; or inclusion of non-ADHD participants in the no-treatment group.

Data Extraction

Eligible studies were reviewed by 2 authors to extract methodological information and statistical information. Smoking outcome data from the longest follow-up period were used in the study. When reported, we extracted the number of smokers (regular smoking, ND) for treated and comparison groups. When these numbers were unavailable, the investigators emailed the authors to request additional information. If the information could not be obtained through this request, the frequencies of smokers/nonsmokers in each group were approximated by using other quantitative information available in the article if possible (eg, percentages, partial information on frequencies of smokers/nonsmokers). Discrepancies across reviewers in calculating the frequencies were resolved through discussion. When articles included only sample size and an OR or HR, the frequencies of smokers/nonsmokers in each treatment group were calculated by using the following procedure: (1) the average percentage of smokers in the untreated samples was calculated across all studies reporting precise frequencies, (2) this average was used to calculate a frequency of untreated smokers for the study in question, and (3) the frequency of smokers in the treated group was input accordingly to replicate the OR/HR reported in the article.

Sample/methodological information extracted from the studies and coded categorically included the following:

Participants

We coded the source of the study sample as follows: community-based

sample, from schools or larger naturalistic studies (0); primary care or outpatient clinic sample (1); and sample referred for psychiatric treatment (2). Average age of participants at follow-up was coded as follows: adolescence (0, approximately half or more of the sample under age 18); adulthood (1, majority over age 18). Percentage of male participants in the sample was included as a continuous covariate.

Intervention

We coded consistency of treatment during the study period as follows: participants who were “ever treated” with stimulants compared with those that were “never treated,” regardless of treatment adherence or duration, or no information available on treatment adherence or consistency (0); treatment group treated consistently throughout the study period or still treated at follow-up (1).

Comparison

Studies were coded for whether analyses accounted for conduct disorder (CD; 1) or not (0).

Outcomes

Smoking outcome measures were coded as follows: “regular”/daily or “current” smoking, positive cotinine screens (0); ND (1).

Study Design

Studies were coded for following participants naturalistically (0) or prospective studies in which participants were evaluated for medication treatment at baseline (1).

Study Quality

Quality was rated by 2 authors using the Ottawa Quality Assessment Scale,⁴⁹ which is used to rate cohort study quality on a 1 to 9 scale with regard to selection of participants (4 criteria), comparability of cohorts (2 criteria),

and assessment of outcome (3 criteria). Interrater discrepancies were resolved through discussion. Quality ratings are reported in Table 1.

Statistical Analyses

Extracted data were entered into RevMan software, version 5.2.⁵⁰ This software used frequencies of smokers/nonsmokers to calculate each study's OR for the association between medication status (medicated versus nonmedicated) and smoking outcomes (regular smoking, yes versus no). An OR of 1 indicates equivalent rates of smoking across the 2 groups; OR < 1 indicates lower smoking in the medicated group; OR > 1 indicates more smoking in the medicated group. We used the Mantel-Haenszel random-effects method to pool the ORs, with 95% confidence interval (CI) to provide information on the precision of measurement. Random-effects models provide more conservative estimates of variance when combining studies with considerable variation in sample and methodology, such as those in the current review. We reported the fixed-effects model for comparison. Heterogeneity was estimated by using the I-square heterogeneity statistic, which estimates the percentage of variability attributed to heterogeneity rather than other sources of error or chance. $I^2 > 50$ and $P < .05$ is considered to indicate significant heterogeneity. Publication bias was assessed by using a funnel plot, which plots each study's effect size against SE, and with Egger's test.⁵¹ We also conducted subgroup analyses by using meta-regression in SAS (SAS Institute, Inc, Cary, NC) to test the contribution of study characteristics to heterogeneity of effect sizes across studies. Meta-regression consisted of simple linear regression by using study methodological attributes to predict study effect sizes (Log[OR]), weighted by the variance of the effect size. A mixed effects model was used with random intercept

parameters controlling study-to-study extra variability.

RESULTS

Figure 1 describes study identification and screening process. We identified 17 studies meeting inclusion criteria in the overall review; sufficient measures and statistical information for inclusion in the meta-analysis were available for 15 of 17 of the studies, and 14 of 17 were included in the meta-analysis (2 studies used the same sample, we included only the longer follow-up⁵²). The 14 studies included a total of 2360 participants with ADHD; 1424 participants were treated with medication and 936 were not. Table 1 shows sample characteristics, methodological attributes, and overall documented effects for the studies. Of 17 studies, one revealed increased rates of smoking with stimulant treatment; nine revealed that stimulant treatment was associated with lower rates or later smoking onset; five revealed no significant association between stimulant treatment and smoking; two revealed an association of stimulant treatment with smoking (1 positive and 1 negative) that was fully accounted for by comorbid CD.

Meta-Analysis

Figure 2 shows ORs and 95% CIs for each study. When comparing samples that were ever treated versus never treated with stimulants and using the closest approximation of regular/daily smoking (Table 1) as the outcome, the pooled random effects OR was 0.54 (95% CI: 0.38–0.78), indicating stimulant-treated youth had lower rates of smoking overall than untreated youth. The OR for the fixed-effects model was 0.61 and statistically significant (95% CI: 0.50–0.76). The funnel plot (Fig 3) was symmetrical aside from 1 outlier, which had a large SE and a large OR. Thus, analyses were also conducted without this outlier with no observed differences in the signifi-

cance level of findings. The bias statistic from Egger's test was nonsignificant ($t = -1.67$, $P = .12$), indicating no significant publication bias.

Significant heterogeneity was detected: $\chi^2(13) = 33.28$, $P < .01$, $I^2 = 61.0$. Results of leave-one-out sensitivity analyses indicated that no single study significantly influenced the pooled OR for the association between stimulant treatment and nicotine use (pooled OR ranged from 0.50 to 0.57, and no 95% CI contained 1).

Moderator Analysis

Participants. Length of study follow-up ranged from 2 to 26 years (median = 7.3 years). Three additional studies used retrospective childhood reports in adulthood. Meta-regression revealed a stronger protective effect of stimulant medication for studies measuring smoking outcomes in adolescence compared with young adulthood ($t[12] = -2.95$, $P < .05$), and for samples with fewer male participants ($t[12] = 4.63$, $P < .001$). Moderation by gender remained significant even after removing the only study with an all-female sample⁵³ ($t[11] = 3.10$, $P < .05$), which was identified as a significant source of heterogeneity in a previous meta-analysis.⁴⁵ The protective effect was also larger for clinical samples compared with community-based samples ($t[10] = 3.68$, $P < .01$), even when controlling for the percentage of male participants, which is often higher in clinical samples. Gender remained significantly associated with effect size in this model ($t[10] = 4.61$, $P < .01$).

Though most studies used samples with a DSM-based ADHD diagnosis, the 2 studies recruiting children under age 10 identified as "hyperactive" were the only 2 studies revealing higher rates of smoking for stimulant-treated children. This effect became nonsignificant when controlling for CD for 1 study,⁵⁴ and the other study did not control for CD.⁵⁵ Thus, these findings may be

TABLE 1 Characteristics of Included Studies

Study	Reported Effect	Sample ^a	Source	Follow-Up	Smoking Measure (Additional)	Consistent Treatment	Accounted for CD	Quality Rating
Biederman et al 2008 ⁵²	Null	<i>n</i> = 140 males, age 6–17, DSM-III	Providers	10 y	ND (onset)	No	Yes ^b	7
Ercan et al 2012 ⁷⁷	Protective	<i>n</i> = 60, ages 7–13, 63% male, comorbid Oppositional Defiant Disorder/CD	Clinical (Tx)	6 y	Current	Yes	Yes ^c	6
Faraone et al 2007 ⁷⁸	Null	<i>n</i> = 206 adults, ~51% male	Community + Providers	Retrospective	ND	Yes	No	5
Groenman et al 2013 ⁷⁹	Null	<i>N</i> = 388, ages 5–17, 81% male	Providers	4 y	ND (onset)	No	Yes	8
Hammerness et al 2013 ⁴⁴	Protective ^d	<i>n</i> = 154, ages 12–17, 74% male; <i>n</i> = 103 community comparison	Clinical (Tx)	2 y	Current/Cotinine	Yes	Yes	7
Huss et al 2008 ⁵⁷	Protective	<i>n</i> = 215, ages >15, 92% male	Clinical (Tx)	Retrospective	Regular (onset, ND)	Yes	Yes ^c	8
Lambert et al 1998 ⁵⁵	Increased risk	<i>n</i> = 221, kindergarten–5th grade, hyperactive, 84% male	Community	26 y	Regular (onset, occasional)	No	No	7
Millberger et al 1997 ¹³	Protective	<i>n</i> = 128, ages 6–17, DSM-III-R, 84% male	Providers	4 y	Regular	Yes ^e	Yes ^b	6
Molina et al 2013 ^{12f}	Protective	<i>n</i> = 420 males, age 7–9, ADHD-C	Clinical (Tx)	8 y	Daily	Yes	No	8
Monuteaux et al 2007 ⁸⁰	Protective	<i>n</i> = 57, age 9–18, 70% male	Providers	<6.5 y	Current/Cotinine	Yes	No	7
Whalen et al 2003 ⁸¹	Protective	<i>n</i> = 27, age 14–15, 85% male, parent-reported diagnosis	Community	2	Current	Yes ^e	No	5
Wilens et al 2008 ⁵³	Protective	<i>n</i> = 114 females, age 6–18	Providers	5 y	ND (onset)	No	Yes	8
Winters et al 2011 ⁵⁴	Increased risk ^d	<i>n</i> = 149, ages 8–10, 81% male, “disruptive” and DSM-III-R	Community	15 y	Regular	No	Yes	8
Upadhyaya et al 2005 ⁵⁶	Protective	<i>n</i> = 84 college adults, 39% male, ADHD symptoms or diagnosis	Community	Retrospective	Regular	Yes	Yes	4
Barkley et al 2003 ^{58g}	Null	<i>n</i> = 147, ages 4–12, 91% male hyperactive	Clinical	8 y	“Ever tried”	No	Yes	7
Biederman et al 1999 ^{82g}	Null	<i>n</i> = 75, age 11–17 males, DSM-III	Providers	4 y	ND	No	Yes ^b	7
Loney et al 2002 ^{83g}	Protective	<i>n</i> = 219 males, age 4–12, hyperkinetic Reaction or Minimal Brain Dysfunction	Clinical (Tx)	10–17 y	Severity 1–3	No	Yes	8

Tx, prospective treatment study.

^a Sample diagnosed with DSM-IV ADHD unless otherwise specified.^b CD was independently associated with smoking outcomes.^c CD reported to be equal across treatment groups but not controlled in analyses.^d CD fully accounted for effects of medication on smoking.^e Majority stimulant-treated, though some individuals received alternative pharmacological or behavioral treatment.^f Additional unpublished data provided by author.^g Qualitative review only, not included in meta-analysis.

explained by conflation of treatment status and CD in hyperactive samples.

Intervention

Seven studies dichotomized the sample into 2 treatment-status groups on the basis of any history versus no history of stimulant treatment. Six studies defined “treated” participants as those maintained continuously on their medication

regimen, and 4 studies divided the treated group into subcategories on the basis of consistency of treatment, such as youth treated before versus after age 12, in the past versus currently, or >50% versus <50% of the time.

Meta-regression revealed larger effect sizes for studies defining treatment as consistent ($t[12] = 2.73$, $P < .05$). Additionally, subgroup analyses revealed

that the pooled OR for studies with consistent treatment was significant (OR = 0.44 [95% CI: 0.32–0.61]) with no significant heterogeneity ($I^2 = 19\%$), whereas the OR for studies comparing ever-treated to never-treated samples was nonsignificant (OR = 0.87 [95% CI: 0.46–1.66]) with significant heterogeneity ($I^2 = 69\%$). Thus, the protective effects of stimulants against smoking

FIGURE 1

Flowchart of study inclusion (preferred reporting items for systematic reviews and meta-analyses).

FIGURE 2

Meta-analysis of ORs of smoking for stimulant-treated individuals with ADHD. aAdditional unpublished data provided by author; results differ from published data.

were only significant for the sub-sample of studies in which participants were consistently treated. Additionally, 1 study revealed that regardless of medication status, individuals whose

ADHD symptoms were well-managed by medication had lower rates of smoking than individuals whose ADHD symptoms continued to exceed clinical thresholds.⁵⁶ Another study⁵⁷ revealed

delayed progression to regular smoking for youth while they were treated.

Comparisons

Thirteen of 17 studies assessed participants for CD, though only nine revealed that CD was incorporated in analyses. CD fully accounted for treatment group differences in smoking in 2 studies, and 3 studies revealed that CD predicted smoking independent of treatment status. Meta-regression indicated larger protective effects of stimulants for studies that controlled for CD ($t[12] = 2.88, P < .05$).

Outcomes

Five studies used DSM-IV diagnosis of ND as the primary smoking outcome variable, whereas 10 studies defined their smoking group as self-described regular smokers (5 studies), current smokers (2 studies) or daily smokers (1 study), or used positive cotinine screens to indicate current smoking (2 studies). Meta-regression revealed no significant difference in effect size for studies that used ND as the outcome compared with regular/current smoking. However, subgroup analyses indicated that the pooled OR for the studies that used ND was nonsignificant ($OR = 0.60$ [95% CI: 0.30–1.23]; $I^2 = 67\%$), whereas the pooled OR was significant for the studies that measured regular smoking ($OR = 0.51$ [95% CI: 0.32–0.80]; $I^2 = 63\%$). In other words, the protective effects of stimulants against smoking were only apparent for the subset of studies that measured regular smoking as opposed to ND. Five studies measured age of smoking onset as an additional outcome variable, and only 1 revealed a significant association between stimulant treatment and later age of smoking onset.⁵³ A study that used ever trying smoking as the primary outcome revealed a null effect.⁵⁸

Study Design

Meta-regression indicated no significant differences in effect sizes for

FIGURE 3
Funnel plot to assess presence of publication bias.

naturalistic studies, in which participants mostly self-selected into treatment-seeking categories, compared with prospective studies in which the entire sample received a medication evaluation and treatment categories were more likely to be defined by physician preferences ($t[12] = -2.05$, $P = .06$). Only 1 study, the Multimodal Treatment Study for ADHD (MTA Study), employed random assignment to medication conditions or included a placebo comparison. At 8-year follow-up, no significant association was reported between ever receiving stimulant treatment and ND diagnosis¹²; however, additional data provided by the author indicated that for youth who continued to take stimulant medication more than 50% of the time at follow-up, medication was associated with lower rates of daily smoking ($OR = 0.51$ [95% CI: 0.27–0.97]).

DISCUSSION

This review constitutes the largest meta-analysis of the relation between stimulant medication treatment and smoking outcomes for ADHD individuals to date, and the first to systematically examine whether methodological attributes moderate effect sizes across studies. We reviewed 17 studies and meta-analyzed

14 to examine the relationship between stimulant treatment of ADHD and cigarette smoking over time. Stimulant treatment was associated with a lower risk for subsequent smoking, with larger protective effects of stimulants in studies that used clinical samples, included more female participants, and conducted follow-up in adolescence as opposed to adulthood. Effect sizes were also larger for studies that defined stimulant treatment as continuous and accounted for comorbid CD in analyses.

Our overall findings differed from those of a previous meta-analysis of 5 studies revealing no significant relationship between stimulant treatment and ND.⁴⁵ A primary difference between the current and previous meta-analyses was that we included studies utilizing a range of smoking outcomes, whereas the previous study focused on studies that measured ND. Although we did not find statistical differences between effects sizes of studies using ND versus measures of regular smoking, the overall protective effect of stimulants against smoking was significant only for the subsample of studies that used measures of regular smoking, and not those that used ND. Thus, our findings are consistent with the previous meta-analysis'

conclusions that stimulant treatment does not have a significant impact on ND diagnosis, and support the notion that multiple measures of smoking are of interest in addition to ND when examining smoking outcomes in adolescent and young adult populations.

Effect sizes were larger for studies that measured smoking in adolescence versus adulthood. Two other meta-analyses^{45,59} revealed a similar age effect for stimulants on drug and alcohol use outcomes. Indeed, young adults have had more time and opportunity to become smokers than adolescents. Another potential explanation is that consistent stimulant treatment may mitigate social risk factors that contribute to smoking in adolescence but are less influential adulthood, such as school failure,⁶⁰ family conflict,⁶¹ or exposure to delinquent peers.⁶² Alternatively, poor parental monitoring and parent–child communication have been found to predict smoking for ADHD adolescents,^{63,64} and treatment-seeking parents may be more engaged in parenting and monitoring. Children who were consistently followed by medical providers for medication management may have also received more oversight and monitoring, thus reducing their risk. Regardless, the protective effects of stimulants to reduce adolescent smoking are clinically relevant, given the association of even occasional adolescent smoking with smoking in adulthood.⁶⁵

The protective effect of stimulants against smoking was stronger for studies that conceptualized treatment as consistent versus those comparing ever-treated to never-treated youth. It is possible that reduced smoking among medicated youth occurs because ADHD symptoms and impairment are effectively mitigated by medication. This notion is consistent with findings of included studies for which symptom management was more predictive of smoking than medication status,⁵⁶ and

consistent medication treatment delayed the onset of smoking.⁵⁷ Further research is needed to better understand aspects of stimulant treatment, such as age of initiation, duration, adherence, or effectiveness, that are associated with positive outcomes for youth, though the current study points to benefits of consistent treatment.

Intervention selection bias, which occurs when the severity of pathology is positively correlated with both treatment status and maladaptive outcomes, is of concern in nonrandomized studies such as most of those included in this review.⁶⁶ For example, youth with more severe externalizing or conduct problems are more likely to smoke⁶⁷ and may also be more likely to be referred for treatment, thus conflating treatment status with smoking. Consistent with this notion, studies that controlled for CD revealed stronger protective effects of stimulants. Indeed, the only study to reveal an iatrogenic effect of stimulants to increase smoking did not control for CD.⁵⁵

Protective effects of stimulants were larger in clinical versus community-based samples. Samples of ADHD youth recruited through treatment referrals often exhibit more deficits than do children with ADHD in the community,⁶⁸ including more severe symptoms, impairment, or comorbidities. Thus, medication effects would be more apparent in clinical samples. Even when accounting for whether the sample was clinical or community-based, we found stronger protective effects of stimulants for samples including more female participants. This finding is consistent with Humphreys et al's⁴⁵ findings for non-specific drug use, though the effect was accounted for by a single study in their analyses. The majority of ADHD treatment studies have focused on men and further research on stimulant treatment, ADHD, and substance use in women is needed.

Limitations

Nearly all studies included in the current review are naturalistic. In the absence of randomization, one cannot identify a causal relationship between stimulants and smoking, or rule out alternative explanations for this association. Youth who received medication may have had greater access to treatment, including parents with more knowledge of ADHD or more opportunities for nonpharmacological treatment. Most of the studies did not provide sufficient data to examine the influence of sample demographics, and this will be an important area for further study. We were also unable to examine differential effects of stimulants on smoking across subtype or severity of ADHD or accounting for comorbidities besides CD. The presentation, symptoms, and impairment associated with ADHD varies greatly across individuals, and some evidence indicates that underlying mechanisms and level of risk of substance use may differ across ADHD subtypes^{69,70} or in the presence of other comorbidities (eg, possible protective effect of anxiety against substance use⁷¹). Furthermore, few of the current studies provided quantitative information on the duration of treatment or age at onset. Future studies may examine the relation of such aspects of treatment to smoking outcomes to help inform clinicians' decisions about when to start and how long to continue treatment.

Our analysis also does not directly address the previously noted discrepancy between laboratory studies of stimulant effects on smoking behavior.^{34–40} Although clinical trials of treatment-seeking smokers with ADHD have shown that neither methylphenidate nor amphetamine increase smoking,^{41,42} studies have not examined how stimulant treatment might influence naturalistic smoking among individuals

with ADHD who are not trying to quit. Such studies are necessary to resolve this discrepancy between laboratory studies and clinical trials of smoking cessation.

Although nearly half of our included studies revealed nonsignificant results and our methods did not suggest publication bias, only published studies on stimulant treatment and smoking were included. Thus, publication bias cannot be eliminated as a possibility.

Implications for Treatment and Prevention

Consistent with previous meta-analyses,^{45,59} our findings indicate that stimulant treatment of ADHD does not increase the risk for smoking and when used consistently, may actually lower such risk. Further research is necessary to identify behavioral and neuropharmacological mechanisms that underlie the observed relation between stimulant medication and smoking, and to rule out extraneous variables that may explain the association. Current findings support the continued use of psychostimulants to improve adaptive functioning in youth with ADHD, and suggest that there may be better results when medication adherence is consistent and symptoms are managed effectively. Unfortunately, treatments for ADHD are highly underutilized⁷² and long-term adherence is poor.^{73–76} Strategies to improve treatment engagement and retention for youth with ADHD may not only maximize the effectiveness of medication, but could have additional benefits to reduce the smoking risk status of this population.

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Address correspondence to Erin N. Schoenfelder, PhD, Department of Psychiatry, 2608 Erwin Rd, School of Medicine, Duke University, DUMC 3527, Durham, NC 27710. E-mail: ESchoenfelder@gmail.com

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