Original Investigation | META-ANALYSIS

Stimulant Medication and Substance Use Outcomes
A Meta-analysis

Kathryn L. Humphreys, MA, EdM; Timothy Eng, BS; Steve S. Lee, PhD

IMPORTANCE Psychostimulant medication is an efficacious treatment for childhood attention-deficit/hyperactivity disorder, yet controversy remains regarding potential iatrogenic effects of stimulant medication, particularly with respect to increasing susceptibility to later substance use disorders. However, stimulant treatment was previously reported to reduce the risk of substance problems.

OBJECTIVE To meta-analyze the longitudinal association between treatment with stimulant medication during childhood and later substance outcomes (ie, lifetime substance use and substance abuse or dependence).

DATA SOURCES Studies published between January 1980 and February 2012 were identified using review articles, PubMed, and pertinent listservs.

STUDY SELECTION Studies with longitudinal designs in which medication treatment preceded the measurement of substance outcomes.

DATA EXTRACTION AND SYNTHESIS Odds ratios were extracted or provided by the study authors. Odds ratios were obtained for lifetime use (ever used) and abuse or dependence status for alcohol, cocaine, marijuana, nicotine, and nonspecific drugs for 2565 participants from 15 different studies.

MAIN OUTCOMES AND MEASURES Random-effects models estimated the overall association, and potential study moderators were examined.

RESULTS Separate random-effects analyses were conducted for each substance outcome, with the number of studies ranging from 3 to 11 for each outcome. Results suggested comparable outcomes between children with and without medication treatment history for any substance use and abuse or dependence outcome across all substance types.

CONCLUSIONS These results provide an important update and suggest that treatment of attention-deficit/hyperactivity disorder with stimulant medication neither protects nor increases the risk of later substance use disorders.

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Author Affiliations: Department of Psychology, University of California, Los Angeles (Humphreys, Eng, Lee).

Corresponding Author: Kathryn L. Humphreys, MA, EdM, or Steve S. Lee, PhD, Department of Psychology, University of California, Los Angeles (UCLA), 1285 Franz Hall, Box 951563, Los Angeles, CA 90095-1563 (k.humphreys@ucla.edu or stevelee@psych.ucla.edu).

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Pharmacotherapy, most often with stimulant medication (eg, methylphenidate and mixed amphetamine salts), is a well-established treatment for attention-deficit/hyperactivity disorder (ADHD)[1] and constitutes the first-line ADHD treatment in many clinical settings.[2] However, the use of stimulant medication to treat ADHD remains controversial given concerns about its potential for abuse[3-5] and possible role in sensitizing patients to later substance problems.[6,7] Treatment with stimulant medication may be related to substance problems for several reasons. Dopamine neurotransmission is featured prominently in current models of stimulant medication and substance use disorders.[8] Nonhuman animal studies[9,10] have implicated methylphenidate administration to a later preference for cocaine. In humans, age of methylphenidate treatment initiation was positively associated with nonalcoholic substance use disorders.[11] These results suggest not only an association between stimulants and substance outcomes but also that neural consequences may differ, depending on the age of exposure.

In the only published meta-analysis on the association of treatment for ADHD with stimulant medication and subsequent alcohol or substance disorders, Wilens et al[12] meta-analyzed 6 studies and concluded that children who received stimulant treatment were significantly less likely to develop alcohol and substance use disorders. However, since this review, results from multiple longitudinal studies[11,13,14] have not found protective effects of stimulant treatment on substance use outcomes. In a recent qualitative review, Golden[15] concluded that inconsistencies in the literature suggest that the predictive validity of stimulant treatment and the development of substance disorders is poorly understood.

Given that 10 years have transpired since the original meta-analysis by Wilens et al[12] and the publication of subsequent multiple studies that failed to replicate the protective effect of stimulant medication treatment for ADHD and substance outcomes, the present meta-analysis included substantially more studies, including several unpublished studies, and investigated both lifetime substance use (ie, ever used) and/or substance abuse or dependence across more substance types (ie, cocaine, marijuana, and nicotine in addition to alcohol and general drug use disorders). Overall, our aim was 2-fold: (1) to meta-analyze the long-term association between medication treatment of children with ADHD (vs children with ADHD not treated with stimulants) and dichotomized measures of lifetime substance use and abuse or dependence across alcohol, cocaine, marijuana, nicotine, and nonspecific drugs (ie, studies that did not provide specific substance type breakdown) and (2) to test theoretically and methodologically relevant moderators if and when significant heterogeneity in effect size was found.

Methods

Study Selection

Each study (with one exception) satisfied the following inclusion criteria: (1) longitudinal design (ie, medication treatment preceded the measurement of substance outcomes), (2) binary measure to identify children with ADHD, (3) binary substance use and abuse or dependence measures, (4) available data to calculate proportions of children with ADHD treated vs not treated with stimulant medication with substance use and abuse or dependence outcomes or reported odds ratios (ORs), and (5) publication between January 1980 and February 2012. In the case of Mannuzza et al,[16] all inclusion criteria were met with the exception of the study population of children with ADHD. Instead, children diagnosed as having a reading disorder who did and did not receive stimulant medication treatment were evaluated. Similar to children with ADHD, children with a reading disorder were more likely to develop an alcohol use disorder than healthy controls.[17] Thus, all individuals in this meta-analysis were at increased risk for substance problems.

Search Procedure

We used several strategies, outlined through the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (eFigure in Supplement), to identify the 15 studies included in this meta-analysis. First, we conducted computer-based searches using PubMed according to the following keywords (or stems when possible): *alcohol, nicotine, smoking, tobacco, cigarette, marijuana, cannabis, cocaine, substance(s), drug(s), ADHD, ADD, attention-deficit, attention-deficit/hyperactivity disorder, hyperactivity, hyperactive, hyperkinetic, stimulant, methylphenidate, pharmacotherapy, medication, longitudinal*, and *prospective*. Keywords were combined by using the Boolean operators "AND" and "OR." Second, we expanded our search through the ancestry approach in which potential studies were identified from the reference sections of relevant studies and reviews pertaining to stimulant treatment and substance disorders. Third, we reviewed the bibliographies for additional studies using forward and backward searching. To combat the file drawer problem, we attempted to locate unpublished studies by sending e-mails describing our study and its inclusion criteria to professional membership listservs of research organizations, including Division 53 of the American Psychological Association and the International Society for Research in Child and Adolescent Psychopathology, and to authors who have published longitudinal studies of children with and without ADHD to determine whether relevant data were available. These efforts yielded 4 unpublished study samples. Although these samples appeared in peer-reviewed publications, the published results were incompatible with the standards outlined in the inclusion criteria (eg, substance outcomes not presented in relation to stimulant treatment). Most reviewed studies were excluded because they were qualitative reviews, substance outcomes were analyzed dimensionally, and/or medication treatment designations did not precede the measurement of substance use. One study that met the inclusion criteria[18] was excluded given author concerns about potential confounds of treatment type in the small sample (Brooke Molina, PhD, written communication, September 2011). Yet another study was excluded[19] given that patients with and without ADHD were included in the frequencies provided for the non-stimulant-treated group. When multiple studies with

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the same substance outcome were derived from the same sample, the most recent publication was used (ie, the longest follow-up period from baseline).

Data Extraction

Three intensively trained raters (K.L.H., T.E., Michael Singer, BA) coded individual studies. Although effort was made to use exact values, we adopted procedures to optimally approximate moderators when precise values were unavailable (eg, taking midpoints of ranges for ages and years if exact information was not provided). Rater agreement for moderator codes was 92%. When raters provided contradictory judgments, disagreements were discussed and the lead author made a final determination.

Moderator Variables

We tested whether potentially important demographic and methodologic factors across the studies moderated the association between stimulant treatment and later substance use and abuse or dependence when heterogeneous effect sizes were detected. The following demographic characteristics were coded: (1) mean age of the sample at follow-up (in years), (2) sex composition (percentage male), (3) racial diversity (percentage white), and (4) mean age of initial ADHD assessment. Methodologic characteristics of each study were coded as follows: (1) percentage of participants with ADHD in the medicated group, (2) sample source (ie, clinic referred vs other), (3) *DSM* version used to determine ADHD status (ie, *DSM-III, DSM-III*-R, or *DSM-IV*), and (4) the mean number of years between the initial assessment and follow-up. Although symptom severity has been associated with substance outcomes,[20] we were unable to include it in any moderator analyses because only 3 studies reported severity of baseline ADHD separately for stimulant-treated youth with untreated youth with ADHD.

Calculation of Effect Size

We calculated the ORs to estimate the effect size of the association between medication status (medicated vs nonmedicated) and 2 separate dichotomous substance outcomes: (1) ever use (yes/no) and (2) abuse or dependence (yes/no). When any cell used to calculate the OR had a value of 0, we inserted 0.5 to all 4 cells to calculate the effect size according to expert recommendation.[21] An OR of 1 indicated that substance outcome was equivalent in children with and without medication treatment history, whereas an OR greater than 1 or less than 1 indicated that the outcome in the medicated group was more or less likely, respectively, to occur in the medicated group. The 95% CI for the OR represents the relative precision of the measurement (ie, wider ranges are less precise). For each study, an OR was separately calculated for each available substance outcome. Thus, the same study could yield as many as 10 ORs, reflecting 5 substance types and use and abuse or dependence. When there was no positive endorsement for the substance outcome, the study was excluded for that outcome. These procedures produced 56 total effect sizes estimated from 15 eligible studies. The number of studies ranged from 3 for nonspecific drug use to 11 for alcohol abuse or dependence. Given that 3 studies is the minimum number required for moderation analysis,[22] subsequent moderator analyses were allowed for all substance outcomes.

Statistical Analysis

Random-effects models were conducted in which the OR for each substance outcome was weighted by the inverse variance of the OR. Heterogeneity of effect sizes was estimated using the standard Cochran Q test, which approximates a χ^2 distribution with $k-1$ df, where k is the number of effect sizes and indicates the degree of consistency of findings across studies.[23] A nonsignificant Q test statistic suggests that the pooled OR represents a unitary effect. When the P value associated with the Q statistic was equal or less than .10, random-effects meta-regression analyses were conducted to determine whether the study characteristics described could explain variability across studies. Publication bias was assessed via the Egger[24] and Begg[25] tests. Leave-one-out sensitivity analyses were conducted when heterogeneous effect sizes were observed. In addition, we examined whether any of the moderator variables predicted significant variance in the effect sizes with significant heterogeneity. The meta-analysis statistical analyses were performed using STATA statistical software (release 11; StataCorp LP).

Results

The **Table** provides descriptive information for each study included in the meta-analysis, including details of demographic and methodologic moderators coded and outcomes obtained.

Alcohol

Four studies evaluated the association between stimulant medication treatment and a lifetime history of alcohol use (ie, having ever used alcohol) among children with ADHD, with ORs ranging from 0.35 to 1.38. For all studies, the 95% CIs included 1. The random-effects meta-analysis found that children who did and did not receive medication treatment were comparable in alcohol use (OR, 0.99; 95% CI, 0.61-1.62; P = .97), and no significant heterogeneity was observed across studies (Q = 2.82, P = .42).

Eleven studies evaluated the association between stimulation medication and alcohol abuse or dependence, with ORs ranging from 0.13 to 3.00 (**Figure 1**). Eight of these studies had 95% CIs that included 1. Two studies[13,36] found that stimulant medication treatment reduced risk of alcohol abuse or dependence, whereas 1 study[31] found that children treated with stimulant medication were significantly more likely to develop alcohol abuse or dependence. The random-effects regression estimated that children with or without medication treatment were largely comparable to alcohol abuse or dependence (OR, 0.80; 95% CI, 0.46-1.38; P = .42), although significant variability was seen in effect sizes (Q = 33.87, P < .001). Follow-up moderator tests are described below.

Cocaine

Three studies evaluated the association of stimulant medication and cocaine use, with ORs ranging from 1.22 to 6.85, and

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Table. Characteristics of Studies Included in the Meta-analysis[a]

Source and No. at Follow-up	Mean Age at Follow-up, y	Male, %	White, %	Sample Source	Stimulant Medication	Age at ADHD Assessment, y	Follow-up Length, y	*DSM* Version	Outcomes
Barkley et al,[26] 2003 (unpublished data)[b]									
Medicated: 98; nonmedicated: 21	15/21/27	87	94	"Referrals to a child psychology service that specialized in the treatment of hyperactive children"	98% Methylphenidate	4-12	7/13/19	Other[c]	AU, CU, MU, NU; AD, CD, MD
Biederman et al,[27] 1999									
Medicated: 56; nonmedicated: 19	15.5	100	100	"Psychiatric and nonpsychiatric settings"	Not provided	6-17	4	*DSM-III-R*	AD, CD, MD, ND
Burke et al (unpublished data)[d]									
Medicated: 95; nonmedicated: 82	17.57	100	70[e]	"Three university outpatient clinics"	93% Methylphenidate	10.02	7.56	*DSM-III-R*[f]	DU, MU, NU; AD, CD, DD, MD, ND[g]
Chilcoat and Breslau,[28] 1999									
Medicated: 30; nonmedicated: 116	11	Not provided	Not provided	"Newborn discharges"	"Nearly all…treated with methylphenidate"	6	5	*DSM-III-R*	DU
Cretzmeyer,[29] 2006[h]									
Medicated: 174; nonmedicated: 37	22	100	98	"Outpatient psychiatric clinic"	100% Methylphenidate	4-12	14	*DSM-IV*	AD, DD
Harty et al,[30] 2011									
Medicated: 69; nonmedicated: 28	18	88	24	"Inner-city population"	Not provided	7-11	9	*DSM-IV*	AD, DD
Hechtman et al,[31] 1984[i]									
Medicated: 20; nonmedicated: 68	21	Not provided	Not provided	"Child psychiatry clinic'	100% Methylphenidate	6-12	"10-12 y follow-up"	Not provided	AD, CD, MD[i]
Huss,[32] 2005; Huss et al,[33] 2008[j]									
Medicated: 106; nonmedicated: 109	21.8	91	Not provided	Clinics in Berlin, Frankfurt, and Cologne	100% Methylphenidate	3-14	12.6	*DSM-III-R* or *DSM-IV*	AU, NU; AD, CD, MD, ND
Katusic et al,[34] 2005									
Medicated: 295; nonmedicated: 84	22	75	96	"Independent School District (ISD) #535"	85.1% Methylphenidate, remaining unspecified	Not provided	16	*DSM-IV*	DD
Lambert and Hartsough,[35] 1998									
Medicated: 93; nonmedicated: 81	17/26[k]	84	77	ADHD referrals from parents, teachers and local treating physicians	Not provided	"Grades kindergarten through 5"	28	*DSM-III-R*	AD, CD, MD, ND
Mannuzza et al,[16] 2003[l]									
Medicated: 39; nonmedicated: 63	26	74	100	"Referred by teachers because of academic difficulties"	100% Methylphenidate	7-13	16	*DSM-III-R*	CU; AD, CD,[m] DD, MD

(continued)

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Table. Characteristics of Studies Included in the Meta-analysis[a] (continued)

Source and No. at Follow-up	Mean Age at Follow-up, y	Male, %	White, %	Sample Source	Stimulant Medication	Age at ADHD Assessment, y	Follow-up Length, y	*DSM* Version	Outcomes
Molina et al,[14] 2007									
Medicated: 239; nonmedicated: 239	11.72	79	61	"Mental health settings, pediatricians, advertisements and school notices"	100% Methylphenidate[n]	7-9.5	3	*DSM-IV*	DU
Owens et al (unpublished data)									
Medicated: 80; nonmedicated: 43	19.7	0	56.4	"Recruited through pediatricians, mental health centers, schools, and direct advertisement"	Not provided	9	10	*DSM-IV*	AU, CU, MU, NU; AD, MD, ND[o]
Wilens et al,[36] 2008									
Medicated: 94; nonmedicated: 20	16	0	95	"Pediatric and psychiatric sources"	Not provided	6-18	5	*DSM-III-R*	AD, DD
Winters et al,[37] 2011									
Medicated: 53; nonmedicated: 67	22	81	93	"22 Suburban elementary schools"	Not provided	7-11	15	*DSM-III-R*	AD, DD,[p] MD, ND

Abbreviations: AD, alcohol abuse or dependence; ADHD, attention-deficit/hyperactivity disorder; AU, alcohol use; CU, cocaine use; CD, cocaine use or dependence; DD, nonspecific drug abuse or dependence; DU, nonspecific drug use; MD, marijuana abuse or dependence; MU, marijuana use; ND, nicotine dependence; NU, nicotine use.

[a] Medication is referred to as stimulant medication throughout, although not all studies provided complete information regarding type of medication used and in some cases only provided the percentage of the sample using selected medication types.

[b] Follow-up at 15 years of age/follow-up at 21 years of age/follow-up at 27 years of age based on the full sample.

[c] Authors report selection criteria have close convergence with *DSM-III-R* or *DSM-IV*.

[d] Substance use assessed annually until 17 years of age, although data may be missing for participants missing an assessment during a year of use.

[e] On the basis of the full sample (participants with and without ADHD).

[f] ADHD designation based on symptom criteria only.

[g] Drug abuse, excluding marijuana and cocaine.

[h] Combined hashish and marijuana.

[i] Abuse or addiction based on period of maximum use.

[j] Translation errors from German may occur.

[k] Nicotine dependence/substance use disorder.

[l] Non-ADHD group: yes/no defined by presence/absence of reading disorders.

[m] Crack cocaine and other stimulants.

[n] For more information, see Multimodal Treatment Study of ADHD Cooperative Group, 1999.

[o] Nicotine dependence defined as daily smoker.

[p] Amphetamines, cocaine, hallucinogens, barbiturates, heroin, inhalants, or club drugs.

all 95% CIs included 1. The random-effects model estimated that children treated with stimulant medication may have higher odds of having used cocaine compared with those who did not receive stimulant medication, but the precision of the estimate is limited, and the 95% CI included 1 (OR, 2.21; 95% CI, 0.87-5.65; $P = .10$). No significant heterogeneity was observed ($Q = 3.27$, $P = .20$).

Seven studies evaluated the association between stimulant medication treatment and later cocaine abuse or dependence (**Figure 2**). The ORs ranged from 0.10 to 2.25, and all 95% CIs included 1. Consistent with these results, the random-effects model estimated that children who received medication treatment were comparable to children who did not receive medication treatment in the development of cocaine abuse or dependence (OR, 1.10; 95% CI, 0.51-2.38; $P = .81$). No significant heterogeneity in ORs was noted ($Q = 8.17$, $P = .23$).

Marijuana

Four studies evaluated the association of stimulant medication and a lifetime history of ever using marijuana, with ORs ranging from 0.73 to 1.37, and all 95% CIs included 1. The random-effects model estimated that children with a history of stimulant medication treatment were comparable to those without (OR, 1.01; 95% CI, 0.68-1.50; $P = .95$). No significant heterogeneity was observed ($Q = 1.85$, $P = .60$).

Nine studies evaluated the association of stimulant medication and marijuana abuse or dependence, with ORs ranging from 0.39 to 4.87 (**Figure 3**). Seven of these studies found no association, whereas 2 studies[27,32] reported that treatment with stimulant medication significantly reduced the risk of developing marijuana abuse or dependence. The random-effects model estimated comparable odds of marijuana abuse or dependence for children who did vs did not receive medication (OR, 0.97; 95%

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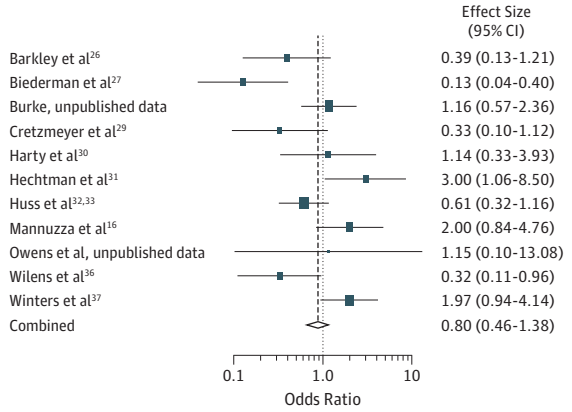
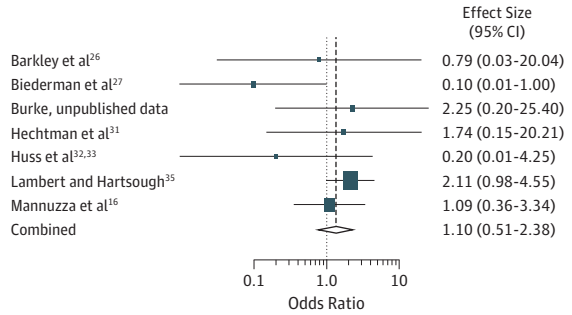
Figure 1. Alcohol Abuse or Dependence



Effect of medication treatment on the risk of alcohol abuse or dependence in children with attention-deficit/hyperactivity disorder.

Figure 2. Cocaine Abuse or Dependence



Effect of medication treatment on the risk of cocaine abuse or dependence in children with attention-deficit/hyperactivity disorder.

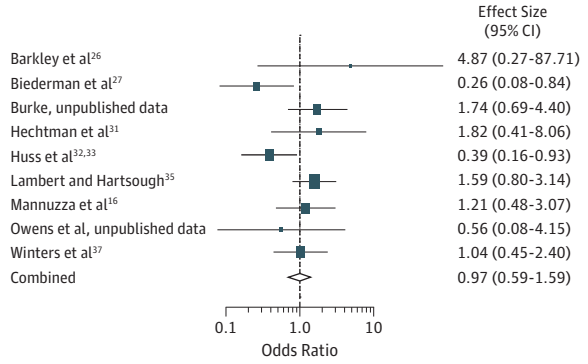
CI, 0.59-1.59; P = .87); however, significant heterogeneity was observed across the studies (Q= 15.68, P = .047).

Nicotine

Four studies evaluated the association between treatment with stimulant medication and ever having used nicotine. The ORs ranged from 0.60 to 2.71, and all 95% CIs included 1. Consistent with this pattern of results, the random-effects model estimated that children with ADHD who received stimulant medication were largely comparable to children not treated with stimulant medication, although the precision of the estimate is limited (OR, 1.55; 95% CI, 0.73-3.30; P = .26). However, there was evidence of significant heterogeneity (Q= 10.72, P = .01).

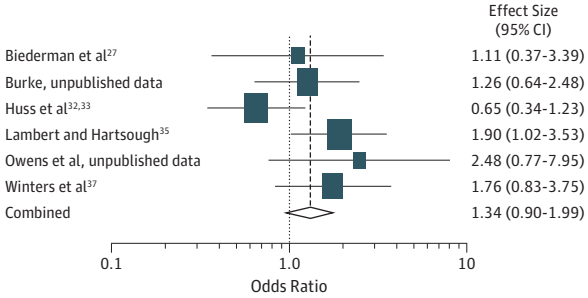
Six studies evaluated the association between stimulant medication treatment and nicotine dependence (**Figure 4**). The ORs ranged from 0.65 to 2.48, with 5 of the 6 studies having reported no significant association and 1 study[35] reporting that treatment of ADHD with stimulant medication increased the risk of nicotine dependence. The overall random-effects model estimated that children who received stimulant medication were comparable to children who did not receive medication

Figure 3. Marijuana Abuse or Dependence



Effect of medication treatment on the risk of marijuana abuse or dependence in children with attention-deficit/hyperactivity disorder.

Figure 4. Nicotine Dependence



Effect of medication treatment on the risk of nicotine dependence in children with attention-deficit/hyperactivity disorder.

treatment in developing later nicotine dependence (OR, 1.34; 95% CI, 0.90-1.99; P = .15). No significant heterogeneity was observed (Q= 7.87, P = .16).

Nonspecific Drug

Three studies evaluated the association of stimulant medication treatment and a lifetime history of nonspecific drug use (defined as a positive endorsement of any illicit drug; used when specific studies did not provide outcome by substance type). The ORs ranged from 1.08 to 1.52. The random-effects model for all studies estimated that children with ADHD who received stimulant medication were similar to children who did not receive stimulant medication in the likelihood of ever having used a nonspecific drug (OR, 1.27; 95% CI, 0.88-1.82; P = .52). No significant heterogeneity was detected across the 3 studies (Q= 0.39, P = .82).

Seven studies evaluated the association of stimulant medication and nonspecific drug abuse or dependence. The ORs ranged from 0.18 to 1.65, with 6 studies having found no significant association and 1 study[36] reporting reduced risk of drug abuse or dependence for children who received medication treatment (OR, 0.18; 95% CI, 0.06-0.50). The random-effects model for all studies estimated that children who received medication treatment were comparable to

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those who did not (OR, 0.85; 95% CI, 0.51-1.40; P = .52), although once again significant heterogeneity was observed (Q= 15.99, P = .01).

Publication Bias

We conducted the Egger and Begg publication bias tests. The bias statistic from the Egger test for marijuana use had a modest association (t = −4.00, P = .06) because the largest study reported a relatively larger effect (stimulant medication treatment was associated with higher rates of ever having used marijuana) than the 3 other studies. No significant publication bias was found for all other substance outcomes.

Given the possibility that unpublished studies differ in rigor, we reanalyzed the substance outcomes with at least 3 remaining contributing studies after the removal of unpublished work. Results were largely consistent with the above analyses, and in all cases the 95% CI included 1.

Leave-One-Out Sensitivity Analyses

Sensitivity analyses were conducted for the 4 outcomes with significant heterogeneity in effects using the leave-one-out approach (ie, running the random-effects model after the removal of each individual study). No single study unduly influenced the OR estimates of the association between stimulant medication treatment and alcohol abuse or dependence (pooled OR estimates, 0.70-0.96; all 95% CIs included 1). For marijuana abuse or dependence, pooled OR estimates ranged from 0.96 to 1.23, and all 95% CIs included 1. The effect size was no longer heterogeneous (P > .05) after the individual removal of 3 studies.[27,32,35] For nicotine use, after the removal of Huss,[32] the effect sizes were no longer significantly heterogeneous (Q= 4.29, P = .12). This study may have contributed to heterogeneity given that the overall estimate from the meta-analysis (Q = 1.55) was not included in the CI range from Huss.[32] Sensitivity analysis for nonspecific drug abuse or dependence found pooled OR estimates ranged from 0.76 to 1.01, and all 95% CIs included 1. The effect sizes were no longer heterogeneous (P > .05) after the removal of one study.[36] When the model was reanalyzed with the study by Wilens et al[36] removed, no significant heterogeneity was found, and the estimated effect was 1.01 (95% CI, 0.70-1.44), suggesting that the study by Wilens et al[36] contributed to the heterogeneous pooled effect size.

Moderators

In addition to leave-one-out analyses, we also explored whether moderators were associated with heterogeneous effect sizes in the 4 substance outcomes identified above. We tested each coded moderator separately using the metareg command for simple regressions. Two moderator variables predicted heterogeneity in effect size in alcohol abuse or dependence. The percentage of children with ADHD treated with stimulant medication (number who received medication/totalnumber of children with ADHD) was negatively associated with pooled effect size (t = −4.25, P = .003, adjusted R^2 = 89.05). As the proportion of those with ADHD who received stimulant medication increased, the OR decreased significantly. In other words, studies with a smaller proportion of individuals treated with stimulant medication were more likely to have those youth meet diagnostic criteria for alcohol abuse or dependence. In addition, as the number of years between initial assessment and the substance use follow-up assessment increased, ORs were larger (t = −4.25, P = .003, adjusted R^2 = 28.91). That is, increased rates of alcohol abuse or dependence were observed for youth treated with medication with longer follow-up. When both moderators were in the same model, only the percentage treated remained a significant predictor of between-study variance. The only other significant moderator variable was for nonspecific drug abuse or dependence, in which the proportion of the sample that was male was positively associated with pooled effect size (t = 2.57, P = .05, adjusted R^2 = 75.81). Notably, the same study[36] removed during the sensitivity analysis appeared to be driving this sex effect. This study included an entirely female sample, whereas all other studies were largely male (74%-100% male). When we reanalyzed the percentage of male participants without the study by Wilens et al,[36] sex was no longer associated with effect size (t = −0.02, P = .99).

Discussion

We meta-analyzed 15 longitudinal studies, consisting of 2565 individuals, to test whether treatment with medication (typically methylphenidate) for ADHD predicted later substance outcomes. Across 5 types of substance (ie, alcohol, cocaine, marijuana, nicotine, and nonspecific drugs) for lifetime use and abuse or dependence, results indicated that substance outcomes were comparable to those individuals who did and did not receive medication. That is, children with ADHD who were treated with stimulant medication were generally equivalent to children with ADHD without stimulant medication histories on all substance outcomes. Moreover, this effect was evident for nicotine and cocaine abuse or dependence, a particularly important consideration given that these outcomes were particularly sensitive to early ADHD in a recent meta-analysis.[38]

These findings diverge from the only meta-analysis on this topic conducted 10 years ago in which stimulant treatment for ADHD significantly reduced later substance problems.[12] Although the original study was based on only 6 studies, it was highly influential as evidenced by its high citation rate and likely affected clinical and scientific attitudes and practice regarding the risk and benefit of treating ADHD with stimulant medication. Crucially, findings from the current meta-analysis, based on a larger sample of studies (including several unpublished studies), suggest no increased or reduced risk of treatment with stimulant medication on later alcohol and substance outcomes and that this pattern was robust to all substance types. In addition to the importance of understanding risk for clinically meaningful outcomes, such as substance abuse or dependence, this study suggests that the likelihood of substance initiation did not differ according to medication status. Given that children with ADHD may have an early substance initiation[20,39] and concern that the use of medication may sensitize youth to

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future substance outcomes, these results find substance use to be unrelated to medication treatment.

Investigators have previously contended[40,41] that the putative protective effect of stimulant medication in the original study by Biederman et al[42] may have instead revealed age-related differences given that older participants simply have greater opportunity to have ever tried substances or to have ever met criteria for substance abuse or dependence. Furthermore, in the more recent study by Biederman et al,[13] hazard ratio CIs included 1 for lifetime alcohol abuse and dependence, drug abuse and dependence, and nicotine dependence at a 10-year follow-up based on stimulant medication treatment status. Age at follow-up remains an important consideration for substance use outcomes because substance patterns may continue to change as individuals enter middle and older adulthood.

Several outcomes in this meta-analysis demonstrated significant between-study variability in effect sizes and thus complicate inferences. Sensitivity analyses and moderator analyses both identified the study by Wilens et al[36] as the source of heterogeneity in effects of stimulant medication and later nonspecific drug abuse or dependence. Unlike the predominantly male samples, this all-female study suggested a potentially protective role of stimulant medication treatment for drug abuse or dependence than did the others. Sex accounted for more than 75% of the variation in effect sizes for this outcome, suggesting that sex differences may be important to consider for stimulant medication and substance use outcomes. Most longitudinal research on ADHD is predominantly male (see the studies by Biederman et al[27] and Hinshaw[43] for key exceptions), and thus the specific effect of treatment among females with ADHD merits further study.

Several important study limitations should be emphasized. First, although the current meta-analysis improved substantially on the heuristic meta-analysis of Wilens et al,[12] it is still relatively modest in terms of the number of studies included. In addition to implementing standard procedures to combat the file drawer problem, we independently contacted several research groups with longitudinal studies of children with ADHD to inquire about potential unpublished data. Although these efforts resulted in the addition of several studies with unpublished data, several investigators did not respond to or declined these requests. Second, the inference that stimulant medication treatment is unrelated to later substance outcomes is based on correlational data. That is, in the absence of random assignment to different treatment groups (eg, with and without stimulant medication), observed group differences may reflect unmeasured confounds. The potential role of intervention selection bias (eg, children with more severe ADHD would be more likely to receive medication treatment) is likely relevant.[44] Given that medication treatment may be biased toward more severe cases,[45] the present findings may indeed represent a protective effect if the group treated with stimulant medication had forgone that medication and developed substance use problems at a higher rate. While we look forward to forthcoming data from randomized controlled studies, such as the Multimodal Treatment Study of ADHD, even these results are qualified given that families from nonmedication treatment arms may obtain medication treatment after randomization. Third, we were limited in the substance outcomes available for meta-analysis in the present literature. Other substance use measures, including frequency or quantity of use, may be meaningful outcomes to examine given limitations with history of use (yes/no), in particular if measurement of substance use is after high school age.[46] Fourth, the issue of comorbidity in ADHD is likely to be salient.[15] Several studies included in the meta-analysis characterized comorbidity among ADHD probands, but few compared whether substance use outcomes based on stimulant medication status differed by comorbidity status or type. Given that externalizing disorders may confound the association between ADHD and substance use outcomes,[47] future research must parse whether the null effects of stimulant medication treatment and later substance outcomes vary by (type of) comorbidity. We urge researchers to include detailed information on outcome by comorbidity so that this information may be examined in future meta-analytic reviews. Fifth, there is evidence that age of treatment initiation is a relevant construct in later substance outcomes because one study found that children who began taking stimulant medication before 8 years of age did not differ in nonalcoholic substance use compared with those without medication treatment, whereas those who began medication treatment after 8 years of age had increased substance abuse.[11] We were unable to thoroughly assess the potential role of age of medication use onset, along with other important and relevant medication-related information thoroughly (type of medication, dosages, medication discontinuation, and treatment adherence) and, importantly, current treatment status. However, future research in this domain must carefully document and examine these potential moderators.

In conclusion, although outcomes from the Multimodal Treatment Study of ADHD indicate that treatment with methylphenidate conferred the largest benefits for ADHD,[48] concern remains over potential adverse effects (eg, effects on height[49]) of treatment with stimulant medication. The present study conducted a rigorous review and update on the empirical literature, prioritizing methodologically rigorous designs (ie, longitudinal) to characterize the association of treatment with stimulant medication and later substance outcomes. Nonhuman animal evidence suggests that adolescent exposure to low-doses methylphenidate resulted in greater cocaine self-administration.[10] However, the ability to draw parallels to human clinical literature remains difficult given the methodologic and developmental differences across species.[50] The present findings do not support the sensitization hypothesis[7,34] as an additional factor in the decision-making process in the treatment of ADHD, although, importantly, the present findings do not support the role of a protective effect for medication treatment for ADHD in both substance use initiation or substance use disorders across a number of substance types. Future work remains to better understand the role of stimulants, if any, on substance use outcomes.

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