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Does Stimulant Therapy of Attention-Deficit/Hyperactivity Disorder Beget Later Substance Abuse? A Meta-analytic Review of the Literature

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Does Stimulant Therapy of Attention-Deficit/Hyperactivity Disorder Beget Later Substance Abuse? A Meta-analytic Review of the Literature

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ABSTRACT. *Objective.* **Concerns exist that stimulant therapy of youths with attention-deficit/hyperactivity disorder (ADHD) may result in an increased risk for subsequent substance use disorders (SUD). We investigated all long-term studies in which pharmacologically treated and untreated youths with ADHD were examined for later SUD outcomes.**

Methods. **A search of all available prospective and retrospective studies of children, adolescents, and adults with ADHD that had information relating childhood exposure to stimulant therapy and later SUD outcome in adolescence or adulthood was conducted through PubMed supplemented with data from scientific presentations. Meta-analysis was used to evaluate the relationship between stimulant therapy and subsequent SUD in youths with ADHD in general while addressing specifically differential effects on alcohol use disorders or drug use disorders and the potential effects of covariates.**

Results. **Six studies—2 with follow-up in adolescence and 4 in young adulthood—were included and comprised 674 medicated subjects and 360 unmedicated subjects who were followed at least 4 years. The pooled estimate of the odds ratio indicated a 1.9-fold reduction in risk for SUD in youths who were treated with stimulants compared with youths who did not receive pharmacotherapy for ADHD ($z = 2.1$; 95% confidence interval for odds ratio [OR]: 1.1–3.6). We found similar reductions in risk for later drug and alcohol use disorders ($z = 1.1$). Studies that reported follow-up into adolescence showed a greater protective effect on the development of SUD (OR: 5.8) than studies that followed subjects into adulthood (OR: 1.4). Additional analyses showed that the results could not be accounted for by any single study or by publication bias.**

Conclusion. **Our results suggest that stimulant therapy in childhood is associated with a reduction in the risk for subsequent drug and alcohol use disorders.** *Pediatrics* **2003;111:179–185;** ***attention-deficit/hyperactivity disorder, substance use, pharmacotherapy.***

ABBREVIATIONS. ADHD, attention-deficit/hyperactivity disorder; SUD, substance use disorders; OR, odds ratio; POR, precision of the odds ratio; SN, standard normal deviate; CI, confidence interval;

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder that is presented for treatment. It is estimated to affect from 4% to 9% of youths.[1–3] Pharmacotherapy in general and stimulants in particular remain a mainstay of treatment for ADHD.[3–7] Data from >200 randomized clinical trials have consistently documented that stimulant drugs are highly effective in the treatment of youths and adults with ADHD.[4–7] A recently published large multisite and randomized study documented the essential role that medication treatment plays in the long-term treatment of children with ADHD.[8]

Despite stimulants' well-documented efficacy in the treatment of ADHD, concerns remain as to whether their use in youths with ADHD could increase the risk for substance use disorders (SUD; denoting drug or alcohol abuse or dependence).[9–13] Although a recent report by our group showed that anti-ADHD pharmacotherapy protected youths with ADHD from later SUD,[14] another study reported just the opposite: cocaine and nicotine abuse were associated with previous stimulant treatment.[15] These contradictory findings call for additional efforts to help resolve this critical issue.

Whether pharmacotherapy for ADHD in general and stimulant treatment in particular leads to SUD in children with ADHD has serious clinical implications given that medications are fundamental in the treatment plan of individuals with ADHD.[3,8] If stimulant therapy for ADHD leads to SUD, then clinicians, patients, and families would need to weigh carefully the risk of SUD against its therapeutic benefits. If, however, stimulant treatment does not lead to SUD, then clinicians, patients, and families could approach pharmacological treatment of youths with ADHD without ungrounded fears of addiction-related complications. Furthermore, if stimulant treatment for ADHD protects against SUD in youths with ADHD, then pharmacotherapy would serve as a preventive approach for SUD risk in youths with ADHD.

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One approach for reconciling conflicting findings among studies is meta-analysis. This method evaluates whether the aggregate evidence across all available studies provides evidence for statistical significance. Thus, to examine the putative association between SUD and previous exposure to stimulants, we applied meta-analysis to all long-term studies in which pharmacologically treated and untreated groups of individuals with ADHD were examined for SUD outcomes.

We tested 3 competing hypotheses. The first was the null hypothesis that stimulant therapy would have no demonstrable effect on the development of SUD in children with ADHD. The second was that exposure to stimulants would predict a higher risk for SUD in general and stimulant and other sympathomimetic abuse in particular. The third posited that stimulant management of ADHD would diminish the later risk for SUD. This hypothesis derives from the idea that SUD in children and adolescents with ADHD may be secondary to ADHD, because of attempts at self-medication[16] or to direct effects of symptoms (eg, impulsivity) and their correlates (eg, poor self-esteem).

METHODS

We conducted a systematic literature search of all available prospective and retrospective studies of children, adolescents, and adults with ADHD that had information on childhood exposure to stimulant pharmacotherapy and data on SUD outcome in adolescence or adulthood. Overall rates of any nonnicotine drug and alcohol use disorder were used. We searched journal articles through PubMed at the National Library of Medicine using ADHD, pharmacotherapy, stimulants, and SUD as key words. This search was supplemented with additional data from scientific presentations at national and international scientific meetings.

We used meta-analyses to evaluate the direction and strength of the overall association, differential effects on drug or alcohol use disorders, and the potential effects of covariates. For the analysis, each study provided the 2×2 table classifying subjects by treatment status (pharmacotherapy [stimulants] or not) and the subsequent development of SUD (present or not) using the odds ratio (OR). For these studies, the OR estimates the increase in the odds of not developing SUD among individuals who were previously treated pharmacologically compared with individuals with ADHD who were not treated pharmacologically. Thus, ORs >1 indicate a protective effect of stimulant therapy on SUD.

Naturalistic studies of psychiatric disorders can lead to the paradoxical result in which greater treatment intensity predicts worse outcome, even when the treatment is known to be efficacious from randomized trials.[17] This paradox occurs because of 2 naturalistic correlations: 1) for many psychiatric disorders, people with more severe disorders are usually given more intense treatments (ie, higher doses or longer duration of treatment); and 2) for many disorders, increasing severity predicts worse outcome. Thus, we assessed studies for evidence of baseline severity differences between the treated and untreated ADHD groups.

We used a random-effects meta-analysis to analyze the ORs using the method of Carlin.[18] To determine whether the results of the meta-analysis were unduly influenced by any 1 study, we recomputed the meta-analysis statistic after deleting each study 1 at a time. Although the meta-analysis accounts for sample size by weighting studies according to their sample size, it does not determine whether the set of published studies shows evidence for the biased publication of positive studies. We addressed this issue using the method of Egger et al.[19] This method is based on the fact that the precision of the OR (POR) increases with larger sample sizes. The methods of Egger et al regresses the standard normal deviate (SND) of the OR (the OR divided by its standard error) against the POR (the inverse of its standard error). In the absence of bias, Egger et al showed that the regression of SND on POR should run through the origin (ie, small samples with low precision have large standard errors and therefore should have small SNDs; large samples have higher precision and smaller standard errors and should have large SNDs). Egger's publication bias statistic is the intercept of the regression, which will be significantly greater than 0 in the presence of publication bias. When the intercept is >0, the smaller studies are finding larger SNDs (and hence larger ORs) than expected. This would occur, for example, if other negative smaller studies had not been published or if they had preferentially published outcomes with large ORs. All analyses used Stata 6.0.[20]

RESULTS

Our literature search revealed a total of 6 studies from the United States and Germany (Table 1). There were 5 prospective longitudinal studies: 2 involving children who were followed at least 4 years[14,21,22] and 3 involving children who were followed into young adulthood (Barkley RA et al, unpublished observations).[15,23–25] One retrospective report was available from a study of adults with ADHD.[26] Overall, these studies comprised 674 medicated subjects and 360 unmedicated subjects. Four of 6 studies demonstrated similar levels of severity and psychiatric comorbidity between the medicated and unmedicated ADHD groups at baseline. For the vast majority of medicated subjects (97%), stimulants (methylphenidate or amphetamine) were used. In 1 study, because no overall rate of drug abuse was reported, rates of cocaine abuse in treated and untreated groups (the only statistically significant finding in substance abuse rates reported in that study) were used as a proxy of overall drug abuse.[15]

For each of the 6 studies, Table 2 gives the ORs that index the protective effect of pharmacotherapy on drug abuse or dependence and their 95% confidence intervals (CIs) and provides the results for alcohol abuse or dependence. The ORs indicate the increased odds of not having an SUD for youths who were treated previously with medication. ORs >1 indicate a protective effect; those <1 suggest that stimulant therapy increases the risk for the SUD outcome. An individual OR is statistically significant at the 0.05 level if its 95% CI does not include 1.0.

As Table 2 shows, 7 of the ORs (from 4 studies) are >1.0, suggesting a protective effect of stimulants. Five of these ORs are statistically significant. Four of the ORs (from 2 studies) are <1, suggesting an adverse impact of stimulants, but these are not statistically significant. The pooled estimate of the OR from the meta-analysis was 1.9 and was statistically significant ($z = 2.1$; $P = .037$; 95% CI for OR: 1.1–3.6). This OR indicates an almost 2-fold reduction in risk for SUD in youths who were treated pharmacologically compared with youths who did not receive pharmacotherapy for their ADHD. There was statistically significant evidence for heterogeneity of the ORs in Table 2 ($\chi^2 = 57.3$; $df = 10$; $P < .001$).

Table 3 presents a sensitivity analysis in which the combined estimate of the OR was computed after omitting 1 data point at a time. This analysis shows whether the significance of the combined estimate can be attributed to a single datum. Table 3 shows that the estimates of the combined OR range from 2.4 to 3.2, suggesting that no 1 study is heavily influencing the combined estimate. Moreover, the confidence

TABLE 1. Description of Studies of ADHD Pharmacotherapy and Later SUD

Study	ADHD (*N*)	Ctrl (*N*)	(+)Med ADHD (*N*)	(−)Med ADHD (*N*)	Age at F/U	Years of F/U	Alc Use Disorder (+)Med (*N* [%])	Alc Use Disorder (−)Med (*N* [%])	Drug Use Disorder (+)Med (*N* [%])	Drug Use Disorder (−)Med (*N* [%])	Baseline Severity Similar?	Comments
24, 25	219	0	182	37	22	15	49 (27%)	21 (56%)	31 (17%)	7 (19%)	Yes	(−)Med with more drug use and more likely to have disorders related to drugs; responders with less SUD than nonresponders; 84% of medicated group Tx > 1 y
15	174	175	93	81	Adult*	>10	41 (44%)	26 (32%)	Marij: 29 (31%); cocaine: 25 (27%); stims: 23 (25%)	Marij: 18 (22.5%); cocaine: 12 (15%); stims: 17 (21%)	No	No overall SUD rates reported; no differences in alcohol, marijuana, stimulants between groups; significant difference in cocaine/tobacco abuse between groups; trend to higher rates of SUD with increased duration of exposure to stimulant
14, 22	190	311	145	45	15.5	4–5	31 (21%)	31 (68%)	23 (16%)	19 (42%)	Yes	Tx duration not assessed; family history of SUD similar between (−)med and (+)med groups; marijuana most common drug of abuse; (+)med with similar risk for SUD as non-ADHD
21	138		53	73	15	5	2 (4%)	15 (21%)	4 (8%)	20 (28%)	Yes	Medication status in adolescence; previous stimulant response did not predict SUD; (−)med 1 y older than (+)meds; marijuana most common drug of abuse
27	206	0	103	103	21	12	NA	NA	10 (11%)	20 (29%)	Yes	Psychotherapy had no effect on drug abuse; medication tx reduced marijuana abuse most robustly; (−)med with earlier onset of alcohol and nicotine use
26	119		98	21	21	15	33 (33%)	7 (33%)	32 (32%)	6 (29%)	No	Only alcohol and cannabis rates reported; no differences in sedatives, stimulants, opiates, and hallucinogens between groups; baseline difference controlled statistically

Tx indicates treatment; (+) meds, youths with ADHD treated pharmacologically; (−) meds, youths with ADHD not treated pharmacologically; F/U, follow-up; alc, alcohol; ctrl, control; stims, stimulants, marij, marijuana; NA, not applicable.
Tx refers to any exposure to agents used in ADHD.
* Age at follow-up not specified.

TABLE 2. Studies That Examined the Impact of ADHD Pharmacotherapy on Later Substance Use Disorders

Study	Protective Effect (OR)	
	OR	95% CI
Meta-analysis of drug studies		
Lambert[15]	0.47	0.22–1.0
Biederman[14]	3.9	1.8–8.1
Huss[26]	2.2	0.99–5.1
Loney[25]	1.1	0.46–2.8
Molina[21]	4.6	1.5–14.5
Barkley	0.83	0.29–2.3
Meta-analysis of alcohol studies		
Lambert[15]	0.6	0.32–1.1
Biederman[14]	8.1	3.9–17.2
Loney[25]	3.6	1.7–7.4
Molina[21]	6.6	1.4–30.2
Barkley	0.98	0.36–2.7

The OR measures the increase in the odds of not having an SUD outcome between medicated and unmedicated youths with ADHD. ORs >1 indicate a protective effect of pharmacotherapy on SUD outcome. The larger the OR, the greater the protective effect of pharmacotherapy on SUD outcome.

TABLE 3. Sensitivity Analysis of Studies

Study Omitted-SUD	Combined Estimate of Protective Effect (OR) After Omission of Study	
	OR	95% CI
Lambert-Alcohol[15]	3.2	1.6–4.9
Lambert-Drug[15]	3.2	1.6–4.9
Biederman-Alcohol[14]	2.4	1.3–3.5
Biederman-Drug[14]	2.9	1.2–4.6
Huss-Drug[26]	3.1	1.3–4.8
Loney-Alcohol[25]	2.9	1.2–4.7
Loney-Drug[25]	3.2	1.5–4.8
Molina-Alcohol[21]	2.6	1.1–4.2
Molina-Drug[21]	2.8	1.2–4.5
Barkley-Alcohol	3.2	1.5–4.8
Barkley-Drug	3.2	1.5–4.9

The OR measures the increase in the odds of not having an SUD outcome between medicated and unmedicated youths with ADHD. ORs >1 indicate a protective effect of pharmacotherapy on SUD outcome. The larger the OR, the greater the protective effect of pharmacotherapy on SUD outcome.

intervals in Table 3 show that the combined OR retains statistical significance regardless of which study is deleted.

We further evaluated factors that potentially influence the SUD outcome. A meta-analysis regression found no effect of type of substance (drug versus alcohol; $z = 1.1$, $P = .3$), but there were significant effects of study design ($z = 2.9$, $P = .004$) and age at follow-up ($z = -4.7$, $P < .001$). The study design effect indicated that studies in which groups of treated and untreated youths with ADHD had similar baseline severity found larger ORs than studies that had dissimilar baseline severity. As a group, the data from studies that had similar baseline severity showed a statistically significant protective effect (OR: 3.5 [2.2, 5.8]). The 4 data points from the 2 studies that did not have similar baseline severity between treatment groups (Barkley RA et al, unpublished observations)[15] both suggest that stimulants increased the risk for SUD outcomes.

The age effect showed that studies that reported follow-up into adolescence[14,21,22] showed a greater protective effect (OR: 5.8) than studies that followed subjects into adulthood (OR: 1.4) (Barkley RA et al, unpublished observations).[15,24–26] The age effect was still significant after removing the 4 data points from 2 studies (Barkley RA et al, unpublished observations)[15] with different baseline severity between treatment groups (OR: 5.8 vs 2.3, $z = 2.7$, $P = .008$).

It is possible that, because of publication bias, the group of studies that controlled for baseline severity overestimates the protective effect of stimulants. However, our analyses found no evidence of such bias. The publication bias statistic was not significant ($t = 0.02$, $P = .99$). Moreover, its value (0.05) was very close to the expected value under the hypothesis that the studies are not biased (0.0).

DISCUSSION

The results of this meta-analysis using data from 6 studies that examined the impact of early medication treatment for ADHD in childhood on subsequent SUD outcome in adolescent and young adult years show that treatment for ADHD significantly decreases the risk for subsequent SUD. These results provide compelling evidence that, contrary to assertions in the popular media, pharmacotherapy with stimulants for ADHD does not lead to SUD but instead seems to have protective effects for adverse SUD outcomes in youths with ADHD.

Examination of individual findings from the 6 studies used in this meta-analysis reveal that 4 (Barkley RA et al, unpublished observations)[14,21,22,24–26] of the 6 available studies identified striking protective effects of stimulant medications for ADHD on subsequent SUD outcome. Two[14,21,22] of these studies that used a comprehensive SUD assessments showed significantly reduced SUD risk in adolescence. Molina and Pelham[21] as part of a comprehensive longitudinal follow-up of children who previously participated in a summer camp for youths with ADHD showed that stimulant treatment in childhood was associated with a reduction in risk for both drug and alcohol use disorders in mid-adolescence. Using data from a longitudinal study of boys with ADHD, our group similarly documented that youths with ADHD who were treated with stimulants (>90% of cases) and other medicines for ADHD in childhood had a 3-fold decreased risk for adverse SUD outcome 4 years later in mid-adolescence compared with youths with ADHD who were not treated pharmacologically.[14,22] Moreover, the risk for SUD did not differ between medicated youths with ADHD and non-ADHD controls. In both the Molina and Biederman studies, comparable reductions in the risk for stimulant, cocaine, and other substances was found in the pharmacologically treated compared with untreated youths with ADHD.

Loney et al[24,25] found significant reductions in the risk for alcohol use disorders in treated youths with ADHD as young adults but failed to identify a similar effect for drug use disorders. The severity of ADHD and rates of comorbidity of this sample were similar between medicated and unmedicated sub-

jects at baseline assessment in childhood. In addition, in an earlier report by this group of investigators based in part on the same cohort, a positive response to treatment was associated with a lower risk for later SUD.[27,28] Likewise, in a systematic retrospective study, Huss[26] reported a clinically and statistically significant reduction in the risk for drug use disorders—in particular, marijuana—in young adults who were treated previously with methylphenidate. The authors found a linear relationship between risk reduction of SUD and duration of exposure to ADHD pharmacotherapy.

Very recently, Barkley et al (unpublished observations) evaluated the outcome for cigarette and substance use as well as SUD. In a longitudinal study of 147 children with ADHD and 73 controls without ADHD who were followed into adolescence (5 years) and young adulthood (15 years), the authors reported no differences in SUD between groups in adolescence or young adulthood. Similarly, the authors found no significant differences in the use of any specific drugs with the exception of cocaine use in adulthood, which was mediated entirely by conduct disorder. A linear effect between risk reduction of hallucinogen and cocaine use disorders and duration of exposure to stimulant treatment was noted, although the effect was mitigated for cocaine abuse when controlling for conduct disorder.

In contrast to these findings that reported protective effects of stimulant treatment for SUD outcomes in adolescents and adults, Lambert et al[15] found that stimulant treatment of ADHD was a risk factor for subsequent drug use disorder in young adults. In particular, exposure to earlier stimulant treatment was linearly related to nicotine and cocaine abuse with notable similar trends to other substance and alcohol abuse. This study, however, had significant differences on baseline characteristics between medicated and unmedicated youths that may have influenced the outcome. For example, conduct disorder is reported in approximately 10% of youths with ADHD.[29] Prospective studies in youths with ADHD have consistently demonstrated that conduct disorder is a major risk factor for the development of early-onset SUD.[30–33] In the study by Lambert et al,[15] conduct disorder was overrepresented in the medicated group.[23] Hence, it remains unclear whether the higher rates of cocaine and nicotine use in the medicated group were a result of the conduct disorder, stimulant treatment, or other variable related to the severity of illness at baseline or follow-up.

Because all of the reviewed studies were naturalistic and, hence, not randomized at baseline to medication, attempts to disentangle positive or deleterious effects of treatment from the severity of the underlying condition(s) are potentially confounded.[17] In all studies in which treated and untreated youths with ADHD had a similar severity at baseline, examination of individual studies[14,21,22,24–26] reveals a reduction in the risk for SUD (Table 2). In contrast, in the 1 study in which SUD was associated with earlier stimulant exposure, severity at baseline was asymmetrically represented in the treated group.[15] Although it is possible that, because of publication bias, the group of studies that controlled for baseline severity overestimates the protective effect of stimulants, our analyses found no evidence of such bias.

Despite[15] findings, this meta-analysis rejects the idea that stimulant therapy of ADHD increases the risk for neither SUD in general nor specific type of alcohol or drug use disorder. Although some preclinical animal models suggest that SUD-related behaviors (eg, preference for sympathomimetic compounds) are associated with early stimulant administration,[9–12] the route and dose of administration of stimulants used in these models may not be applicable to human data.[34,35] For example, in preclinical studies with rats, methylphenidate was often administered intraperitoneally at supratherapeutic human dosing equivalence.[9,10] Given that parental administration of methylphenidate exceeds oral dosing,[36,37] the dosing in animals is in excess of the upper limit of therapeutic dosing recommended in humans.[4,6]

Our finding of a less robust protective effect of ADHD pharmacotherapy in reducing SUD in adulthood (OR: 1.4) relative to adolescence (OR: 5.8) is noteworthy. Although data on duration of exposure to pharmacotherapy were not available, it is possible that the adult samples—because of dated recommendations to discontinue treatment in adolescence[38]—had experienced more years without treatment than the adolescent samples. If so, then it may be that lack of medication coverage in adulthood reduced the overall protective effect of earlier stimulant treatment. Alternatively, enhanced parental monitoring of youths who receive medications may have a preferential effect in adolescents compared with young adults. It may also be that adolescents have not fully passed through the age of risk to develop SUD given that retrospectively derived data from adults indicate that the mean onset of SUD is at 19 years in individuals with ADHD.[39] Clearly, more work to disentangle these issues is warranted.

ADHD has been shown to be a risk factor for cigarette smoking in children[40,41] and adults.[42] Although the current meta-analysis lacked adequate power to evaluate stimulant exposure and cigarette smoking, notable trends emerged in studies that examined this issue. One study in adults by Lambert et al[15] found a linear increase in smoking related to stimulant exposure in individuals with ADHD. In contrast, 1 study in adolescents[21] and 1 study in adults[24,25] reported that the risk for stable tobacco use was higher in individuals with ADHD who were not receiving stimulant treatment. No effect of stimulant treatment of ADHD on later risk for cigarette smoking was reported in 1 study of adolescents[14,22] and 1 in adults (Barkley RA et al, unpublished observations). Hence, reminiscent of findings on SUD, the aggregate literature seems to support that stimulant pharmacotherapy of ADHD is not related to an increased risk for subsequent cigarette or tobacco abuse.

The mechanism by which ADHD stimulant pharmacotherapy protects against SUD remains unclear. It may be that the reduction of ADHD symptoms,

demoralization, poor self-esteem, and academic or occupational failure associated with ADHD[43–45]—factors associated independently with SUD risk[46–49]—results in reduced SUD. It may also be that by their pharmacological efficacy in diminishing conduct symptoms,[50] the stimulants may have indirectly reduced the risk for SUD by reducing the risk that conduct imparts on SUD. Families who seek medication treatment for their youths may be more intact or of higher socioeconomic status, more invested in their children's education success, or more involved in their parenting. Alternatively, the close monitoring of youths who receive medications may directly influence SUD risk, independent of the actual medication effect, as has been purported elsewhere.[40] Additional research to evaluate the connection between symptom expression, self-esteem, and functional status and later SUD in individuals with ADHD is necessary.

Our finding that ADHD pharmacotherapy protects against later SUD is of high clinical and public health relevance. Clinically, the absence of evidence linking SUD with stimulant medication should reassure clinicians and families when discussing the risks and benefits of medication intervention for ADHD. The apparent effect of stimulant treatment of ADHD reducing SUD is among the most robust findings in pediatric mental health indicating a protective effect of treatment on lessening SUD risk. The mechanism of treatment in general and medication management in particular as a protective factor against SUD in ADHD could serve as a template for other mental health disorders. From the public health perspective, given the high prevalence of ADHD in youths and their high risk of developing SUD,[44,51–56] the identification and treatment of youths with ADHD may affect a large segment of the adolescent and young adult population culpable to SUD.

The results from this meta-analysis need to be tempered against their limitations. In general, there was a paucity of research data available for review ($N = 6$ studies). However, meta-analytic techniques derive statistical power to detect group differences from the size of the individual studies in the analysis. The total number of treated and untreated subjects with ADHD across all studies was substantial ($N = 1034$), suggesting that our findings are not a result of low power. Although our finding of no publication bias could be attributable to low power, the value of the publication bias statistic was so close to 0 (the no bias value) that it is reasonable to assert that bias may not have been an issue.[19]

The naturalistic nature of the studies may have created confounds (eg, severity of illness, family history of SUD) that may have independently affected outcome. For example, families with a history of SUD may be less inclined to place their children on medication, providing a potential bias for SUD in the untreated groups. In contrast, more severe cases of ADHD may be referred for pharmacotherapy, biasing the treated groups to SUD. Ideally, such biases would be handled with long-term, randomized, controlled trials, but because such trials are not ethical, research in this area must rely on naturalistic designs.

Adolescents with ADHD may not have passed through the full risk for developing SUD. Hence, our findings may have been biased by the more robust reduction in SUD associated with earlier stimulant treatment that was observed in the adolescent studies (OR: 5.8) relative to the adult studies (OR: 1.4). The majority of youths with ADHD on whom data were available were male, limiting the generalization of these findings to female individuals with ADHD. Although the vast majority of youths with ADHD were treated with stimulants, a small minority (3%) of the medicated group received nonstimulant medications for their ADHD. SUD outcome relied on self- or parental report, and the criteria used to denote abuse or dependence of substances varied between studies. Most studies did not elaborate on the relationship of SUD to the duration of medication exposure or adequacy of treatment. Because stimulants were the most common class of medications used for ADHD, the effects of other classes of medication on SUD outcome remain unclear.

Despite these limitations, a meta-analysis of the available literature indicates that stimulant therapy of ADHD does not increase the risk for subsequent SUD but seems to have a protective effect. Additional studies to investigate the long-term SUD outcome and putative mechanism(s) of reduced SUD risk in youths of both genders with ADHD treated pharmacologically are necessary.

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