ADHD Medication and Substance-Related Problems

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Objective: Substance use disorders are major contributors to excess mortality among individuals with attention deficit hyperactivity disorder (ADHD), yet associations between pharmacological ADHD treatment and substance-related problems remain unclear. This study investigated concurrent and long-term associations between ADHD medication treatment and substance-related events.

Method: The authors analyzed 2005–2014 commercial health care claims from 2,993,887 (47.2% female) adolescent and adult ADHD patients. Within-individual analyses compared the risk of substance-related events (i.e., emergency department visits related to substance use disorders) during months in which patients received prescribed stimulant medication or atomoxetine relative to the risk during months in which they did not.

Results: In adjusted within-individual comparisons, relative to periods in which patients did not receive ADHD medication, male patients had 35% lower odds of concurrent substance-related events when receiving medication (odds ratio=0.65, 95% CI=0.64–0.67), and female patients had 31% lower odds of concurrent substance-related events (odds ratio=0.69, 95% CI=0.67–0.71). Moreover, male patients had 19% lower odds of substance-related events 2 years after medication periods (odds ratio=0.81, 95% CI=0.78–0.85), and female patients had 14% lower odds of substance-related events 2 years after medication periods (odds ratio=0.86, 95% CI= 0.82–0.91). Sensitivity analyses supported most findings but were less consistent for long-term associations among women.

Conclusions: These results provide evidence that receiving ADHD medication is unlikely to be associated with greater risk of substance-related problems in adolescence or adulthood. Rather, medication was associated with lower concurrent risk of substance-related events and, at least among men, lower long-term risk of future substance-related events.

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Attention deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder, affecting 2.6%−4.5% of youths worldwide and continuing, for many, into adolescence and adulthood (1–3). Prospective studies show that the risk of substance use disorders is a persisting concern in ADHD (4, 5) at least in part because the two disorders share genetic influences (6–8). Substance use disorders contribute substantially to elevated mortality rates among patients with ADHD (9).

Understanding the association between pharmacological ADHD treatment and substance-related problems is essential for evaluating the potential benefit of such treatment. Stimulant medications are effective in reducing ADHD symptoms in the short term and are recognized as the first-line treatment option for school-aged children, adolescents, and adults (10–12). Medication associations with substance-related problems, however, have been widely debated (13). Some early research suggested a sensitization hypothesis, wherein exposure to stimulants might increase risk for substance-related problems (14). This possibility continues to be supported by some animal studies, particularly during adolescence (15). Further clinical studies, in contrast, have not found support for medication-induced increases in risk. For example, follow-up data from the Multimodal Treatment Study of Attention Deficit Hyperactivity Disorder and a meta-analysis showed no medication associations with substance use or problems (16, 17). In fact, several more recent studies have found that medication treatment is associated with decreased substance-related risk (18–20). At present, uncertainty remains regarding the extent to which medication treatment affects substance-related problems (21–24).

Conclusions from randomized clinical trials have been constrained by sample sizes and treatment durations that may be insufficient to detect rare but serious substance-related events, questions regarding generalizability, and ethical concerns about withholding efficacious treatments (24, 25). At the same time, conclusions from observational studies have been constrained by the possibility of confounding from differences between patients who are and are not treated pharmacologically (i.e., confounding by indication) (16).

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Consequently, researchers have turned to observational approaches that combine large-scale health record data with designs that make within-individual comparisons across medicated and unmedicated periods, treating each patient as his or her own control (26, 27). Notably, Chang and colleagues (19) found that risk of substance-related problems was lower when ADHD patients in the Swedish population were prescribed stimulant medications. That study additionally found a long-term association between medication and lower risk for later substance-related problems, using statistical covariates but not within-individual comparisons. Given cross-national differences in diagnostic and treatment practices, the extent to which these results will generalize to other settings is unclear, and the possibility of unmeasured between-persons confounding renders the long-term associations less conclusive. In the present study, we used within-individual comparisons in a large U.S. sample to examine the extent to which stimulant and atomoxetine treatment for ADHD was associated with concurrent and long-term reductions in risk of substance-related events.

METHOD

Sample

We used data from the Truven Health MarketScan® Commercial Claims and Encounters (MarketScan) databases of de-identified inpatient, outpatient, and prescribed drug claims. As confirmed with the University of Chicago institutional review board, the analysis of MarketScan data is exempt because records are de-identified. Data were available from 2003 through 2014, although we analyzed patients identified in years 2005–2014 because emergency services coding was incomplete in earlier years. MarketScan includes data from employers and health plans in the United States. From 2005 onward, there are approximately 146 million unique enrollee observations in MarketScan, consisting of employees, individuals receiving COBRA benefits, non-Medicare retirees, and covered spouses and dependents.

We identified 2,993,887 (47.2% female; Table 1) ADHD patients, defined as enrollees who received either an ADHD diagnosis (ICD-9 codes 314.xx) or stimulant or atomoxetine ADHD medication treatment. We defined as the index date the first inpatient or outpatient diagnosis or filled prescription from 2005 onward. We followed each patient from the index date until his or her last month with any enrollment days or until December 2014. However, because substance-related problems in childhood are rare, we analyzed only those enrollment periods in which patients were at least 13 years old. We excluded all enrollment years in which patients lacked prescription drug coverage. If patients disenrolled and subsequently re-enrolled, we included continuous follow-up through the first disenrollment.

ADHD Medication

We identified stimulant medications using national drug codes for the following generic names: amphetamine salt combination, dexmethylphenidate hydrochloride, dextroamphetamine sulfate, lisdexamfetamine dimesylate, methamphetamine hydrochloride, methylphenidate, and methylphenidate hydrochloride. Atomoxetine hydrochloride was the only included nonstimulant medication because other approved nonstimulants (i.e., extended-release clonidine and guanfacine) are frequently used as adjunctive or secondary treatments (11). We required prescription claims to have valid fill dates and days of supply (180 days or less). Medication status was defined on a monthly basis, such that a calendar month covered at least in part by a prescription (i.e., fill date plus days of supply) was considered medicated, whereas a month not covered by any prescription was considered unmedicated. Most male (83.5%) and female (87.2%) patients received ADHD medication during at least 1 follow-up month (Table 1). Among these patients, most male (89.2%) and female (90.9%) patients received stimulant medication only.

Substance-Related Events

Within-individual comparisons require a time-specific outcome. To exclude recurring treatment visits and ensure that claim dates corresponded with actual substance-related events, we counted follow-up months as having an event if they had at least one emergency department claim with any non-tobacco-related substance use disorder diagnosis (primary or otherwise). For details, see the Supplemental Method section in the data supplement that accompanies the online edition of this article.

Analytic Approach

We made three sets of comparisons using SAS, version 9.4 (SAS Institute, Cary, N.C.). We report associations separately for male and female patients because concurrent within-individual associations significantly differed by sex (long-term associations did not differ significantly). The first comparisons examined purely between-individual group differences. We used conditional logistic regression to compare the risk of at least one substance-related event from 2005 onward among ADHD patients with that among non-diagnosed, nonmedicated controls matched 1:1 on sex, calendar year of first enrollment in MarketScan, age of first enrollment, and length of enrollment in months (PROC LOGISTIC; more than 99.9% of patients could be matched). We then compared those ADHD patients who received any ADHD medication with those who never received medication from 2005 onward (controlling for year of first enrollment, age of first enrollment, and enrollment length).

The second set of comparisons examined concurrent associations between ADHD medication and substance-related events. We structured follow-up time by months and compared the risk of substance-related events during months in which patients were or were not prescribed ADHD medication (28). We analyzed substance-related events as repeating outcomes, permitting individuals to experience multiple months with events during follow-up. Events that occurred during the index month were counted only if they

occurred after the index date. In a small number of instances (N=2,634; 0.004% of included months), patients began new prescriptions and experienced substance-related events in the same month. In these cases, we considered patients as unmedicated for the 47.2% of months in which the patient's first substance-related event occurred before or on the same date as that patient's first prescription fill.

We began with population-level models. These models compared medicated periods with unmedicated periods, adjusting for the clustering of months within individuals using PROC SURVEYLOGISTIC. We report odds ratios with and without time-varying covariates (age, calendar year, and time since last substance-related event). Population-level models remained susceptible, however, to unmeasured confounding factors that differentiated patients who received ADHD medication from patients who did not. For our primary analyses, we therefore estimated associations using purely within-individual conditional logistic regression. These models compared months in which an individual received medication with months in which that same individual did not receive medication. Because each individual served as his or her own comparison, these models were free of confounding from all factors that were constant within the individual over time (e.g., genetics, earlier environmental influences) (29). Because the relatively small changes in years of age or calendar year that occurred during follow-up were unlikely to affect within-individual risk of substance-related events, we controlled for time since last event only.

Ten sensitivity analyses explored the robustness of the within-individual associations (see the Supplemental Method section in the data supplement). The first sensitivity analysis examined patients who already had any claims with substance use disorder diagnoses at or before the start of follow-up. The second and third analyses excluded patients who received other psychiatric medications or psychotherapy, respectively, in order to test whether the results were explained by other treatments. The fourth analysis tested whether results would persist in newly treated patients by examining a cohort with incident diagnoses of ADHD after at least 1 year of enrollment. The fifth analysis examined only the first substance-related events in this incident diagnosis cohort, which reduced the likelihood of bias due to increased medication treatment following prior substance-related events (i.e., reverse causality). The sixth analysis defined treatment gaps more conservatively by coding the first month after a medication period as still medicated. The seventh analysis examined stimulant medications only. The eighth analysis examined a broader definition of substance-related events that also included inpatient and ambulance claims. The ninth analysis estimated associations separately by age group given questions about developmental timing. Finally, to evaluate the specificity of the association to ADHD medication, the 10th analysis used selective serotonin reuptake inhibitors (SSRIs) as a negative control medication exposure (27, 30).

The third set of comparisons examined long-term (i.e., interval) associations. The interval associations tested whether medication status at a given month predicted differences in the risk of substance-related events at an interval of 2 years later. We included concurrent and lagged medication status as predictors, ensuring that the lagged association was independent of concurrent medication. We required patients to have at least 2 years of follow-up for these models and, because their lagged exposure status would otherwise be undefined, we necessarily excluded all months prior to 2 years of follow-up. We again repeated these models at the population and within-individual levels. In addition to those described above, sensitivity analyses also examined a 3-year interval and the duration of medication exposure (i.e., the cumulative months of medication during the prior 2 or 3 years).

TABLE 1. Summary Statistics for ADHD Patients in a Study of ADHD Medication and Substance-Related Problems[a]

Variable	Male		Female	
	N	%	N	%
Included patients	1,579,704	–	1,414,183	–
Medicated at least 1 month	1,319,349	83.5	1,233,425	87.2
At least one medication status switch	910,084	57.6	811,050	57.4
At least one substance-related event	34,655	2.2	24,196	1.7
	Median	IQR	Median	IQR
Age in years at start of follow-up	21	15–34	28	19–42
Follow-up months	16	8–33	15	8–31

[a] Patients with at least one medication status switch had at least 1 month with filled prescription coverage as well as at least 1 month with no prescription coverage. Observed ages ranged from 13 to 64 years at start of follow-up, and observed follow-up ranged from 1 to 120 months. ADHD=attention deficit hyperactivity disorder; IQR=interquartile range.

RESULTS

Group Comparisons

Male (3.2%) and female (2.6%) ADHD patients were more likely to have at least one substance-related event than were male (1.2%; odds ratio=2.69, 95% CI=2.65–2.74) and female (0.8%; odds ratio=3.30, 95% CI=3.23–3.37) controls. Male ADHD patients who ever received medication were less likely to have substance-related events (3.1%) than were those who never received medication (4.0%; odds ratio=0.76, 95% CI=0.75–0.78). There was less difference in the odds of substance-related events among female patients who received medication (2.6%) relative to those who never received medication (2.8%; odds ratio=0.94, 95% CI=0.91–0.97). Although claims with any substance use disorder diagnosis were more common than were claims with emergency substance-related events, group differences in risk of any diagnosis were comparable (see Table S1 in the online data supplement).

TABLE 2. Concurrent Associations Between ADHD Medication and Substance-Related Events[a]

			Population				Within-Individual			
			Unadjusted		Adjusted		Unadjusted		Adjusted	
Cohort	Patients (N)	Substance-Related Events (N)	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Male										
All ADHD patients	1,579,704	46,676	0.68	0.67–0.70	0.81	0.79–0.83	0.79	0.77–0.81	0.65	0.64–0.67
With any prior substance use disorder	53,765	10,671	0.70	0.67–0.75	0.77	0.73–0.81	0.94	0.89–1.00	0.85	0.79–0.90
With no prior substance use disorder	1,525,939	36,005	0.74	0.72–0.76	0.86	0.84–0.88	0.76	0.74–0.78	0.61	0.59–0.63
With no other psychiatric medications	836,305	8,506	0.72	0.69–0.76	0.82	0.79–0.86	0.78	0.73–0.83	0.61	0.58–0.66
With no psychotherapy	1,129,582	17,360	0.78	0.75–0.80	0.87	0.84–0.90	0.79	0.75–0.82	0.58	0.56–0.61
Incident diagnosis cohort	304,467	9,647	0.72	0.68–0.76	0.79	0.75–0.83	0.85	0.80–0.91	0.75	0.70–0.81
First events only	304,467	7,128	0.85	0.81–0.89	0.81	0.77–0.85	0.45	0.41–0.49		–
Female										
All ADHD patients	1,414,183	31,842	0.81	0.79–0.84	0.89	0.87–0.92	0.84	0.81–0.86	0.69	0.67–0.71
With any prior substance use disorder	37,985	6,712	0.69	0.64–0.74	0.72	0.68–0.76	0.83	0.77–0.89	0.74	0.69–0.80
With no prior substance use disorder	1,376,198	25,130	0.89	0.86–0.91	0.97	0.94–0.99	0.84	0.81–0.87	0.67	0.65–0.70
With no other psychiatric medications	481,157	3,237	0.94	0.87–1.01	0.98	0.91–1.06	0.91	0.81–1.01	0.74	0.66–0.82
With no psychotherapy	963,074	10,694	0.97	0.93–1.02	1.01	0.97–1.05	0.90	0.85–0.95	0.66	0.62–0.70
Incident diagnosis cohort	251,990	5,685	0.87	0.82–0.93	0.89	0.84–0.94	0.94	0.87–1.03	0.87	0.80–0.95
First events only	251,990	4,406	1.01	0.95–1.07	0.96	0.90–1.02	0.57	0.52–0.64		–

[a] Adjusted models control for age and calendar year (population models), time since last substance-related event (population and within-individual multiple events models), and months since index date (population first events models only). ADHD=attention deficit hyperactivity disorder.

Concurrent Associations Between ADHD Medication and Substance-Related Events

The second set of comparisons examined concurrent associations between receiving ADHD medication prescriptions and risk of substance-related events. At the population level, the adjusted odds of substance-related events were 19% lower among male patients (odds ratio=0.81, 95% CI=0.79–0.83) and 11% lower among female patients (odds ratio=0.89, 95% CI=0.87–0.92) during medicated months relative to unmedicated months (Table 2). More importantly, in within-individual comparisons that ruled out all time-invariant confounding effects, patients were less likely to have substance-related events during the specific months in which they received medication relative to months in which those same patients did not receive medication. Specifically, in adjusted models, ADHD medication was associated with 35% lower odds of substance-related events among men (odds ratio=0.65, 95% CI=0.64–0.67) and 31% lower odds among women (odds ratio=0.69, 95% CI=0.67–0.71). Table S2 in the online data supplement lists covariate parameter estimates.

Sensitivity analyses. Sensitivity analyses supported these associations. Among patients with prior diagnoses of substance use disorder, the concurrent associations were somewhat attenuated but remained statistically significant, except in the unadjusted model for male patients (Table 2). When we included only patients without other psychiatric medications or psychotherapy or with incident ADHD diagnoses, the associations remained in the same direction, although unadjusted associations for female patients without other medications or incident diagnoses did not reach statistical significance. Notably, in within-individual models of first substance-related events only, medication was associated with 55% and 43% lower odds of events among male and female patients, respectively, suggesting that results from the repeated event analyses may be conservative estimates of ADHD medication associations.

Defining medication gaps more conservatively, including stimulant medication only, and including inpatient and ambulance claims as substance-related events all produced comparable associations (see Table 3, which also shows results across ages). Although their point estimates varied, the within-individual associations remained in the same direction in all age groups (and were statistically significant in adjusted models). Finally, and critically, the within-individual associations between SSRIs and substance-related events were positive, supporting the specificity of the associations for ADHD medication.

Long-Term Associations Between ADHD Medication and Substance-Related Events

The third set of comparisons examined associations with substance-related events 2 years later. Adjusted population models showed minor increases in risk of substance-related

TABLE 3. Sensitivity Analyses for Concurrent Within-Individual Associations Between ADHD Medication and Substance-Related Events[a]

Sensitivity Analysis	Patients (N)	Substance-Related Events (N)	Unadjusted		Adjusted	
			Odds Ratio	95% CI	Odds Ratio	95% CI
Male						
1-month extended medicated periods	1,579,704	46,676	0.82	0.80–0.84	0.67	0.66–0.69
Stimulant medication only	1,579,704	46,676	0.80	0.78–0.82	0.66	0.64–0.68
Ambulance, inpatient, or emergency events	1,579,704	80,653	0.77	0.76–0.79	0.71	0.69–0.72
Age[b]						
13–17	615,297	18,410	0.69	0.66–0.72	0.61	0.59–0.64
18–25	366,021	15,566	0.97	0.92–1.01	0.77	0.74–0.81
26–35	236,249	4,961	0.81	0.74–0.88	0.57	0.52–0.63
36–45	174,849	3,690	0.77	0.70–0.86	0.62	0.56–0.69
46+	187,288	4,049	0.69	0.62–0.76	0.55	0.49–0.61
SSRI medication	1,579,704	46,676	1.34	1.30–1.39	1.42	1.37–1.47
Female						
1-month extended medicated periods	1,414,183	31,842	0.90	0.87–0.93	0.74	0.71–0.76
Stimulant medication only	1,414,183	31,842	0.85	0.82–0.88	0.70	0.68–0.72
Ambulance, inpatient, or emergency events	1,414,183	54,420	0.79	0.77–0.81	0.71	0.69–0.73
Age[b]						
13–17	299,018	8,714	0.85	0.80–0.90	0.77	0.73–0.82
18–25	333,016	9,767	0.98	0.93–1.04	0.78	0.74–0.83
26–35	266,275	4,485	0.80	0.74–0.88	0.60	0.55–0.65
36–45	241,620	4,384	0.67	0.61–0.73	0.54	0.50–0.60
46+	274,254	4,492	0.72	0.66–0.79	0.56	0.51–0.62
SSRI medication	1,414,183	31,842	1.22	1.18–1.27	1.25	1.20–1.30

[a] Adjusted models control for time since last substance-related event. ADHD=attention deficit hyperactivity disorder; SSRI=selective serotonin reuptake inhibitor.
[b] Age group in years at start of follow-up.

events among male (odds ratio=1.02, 95% CI=0.99–1.06) and female (odds ratio=1.10, 95% CI=1.05–1.15) patients 2 years after medicated periods. However, in adjusted within-individual models, ADHD medication predicted a 19% reduction in the odds of substance-related events 2 years later among male patients (odds ratio=0.81, 95% CI=0.78–0.85) and a 14% reduction among female patients (odds ratio=0.86, 95% CI=0.82–0.91) (see Table 4, which also presents the concurrent medication estimates from the long-term models).

Sensitivity analyses. We examined long-term associations among patients without other psychiatric medication, without psychotherapy, or with incident ADHD diagnoses. For male patients in all three groups, medication was associated with reduced long-term, within-individual risk of substance-related events. In contrast, female patients displayed attenuated long-term associations (4%−7% reductions, which were not statistically significant) among those without other medications or with incident ADHD diagnoses, but they displayed a 17% reduction in the odds of later substance-related events among those without psychotherapy. Long-term associations without adjustment for time since last event persisted among men but were attenuated among women (see Table S3 in the online data supplement).

Table 5 presents additional sensitivity analyses for the adjusted long-term associations. In male patients, we found largely comparable associations when we examined cumulative prior medication exposure, 3-year rather than 2-year time intervals, stimulant medications only, and the broader substance-related event definition. Associations for female patients persisted in some, but not all, analyses. In addition, the adjusted associations remained in the same direction in all age groups in both sexes, although they were not all statistically significant, likely in part because of decreased power. Finally, SSRIs were associated with minimal differences in the odds of later substance-related events among male and female patients.

DISCUSSION

To our knowledge, this national U.S. study is the largest to date to examine whether stimulant and nonstimulant medication therapies for ADHD—widely used and efficacious in the short term for core ADHD symptoms—are associated with differences in risk of substance-related problems. Medication periods were generally associated with reduced risk of substance-related events. Among male patients, these associations held concurrently, in the long term, across most ages, and across multiple sensitivity analyses. Among female patients, many sensitivity analyses supported a concurrent association, but some failed to support a long-term association with reduced risk. Even when the results failed to support reductions in risk, we found almost no evidence that medication increased risk of substance-related events, including among those with pre-existing substance use disorders.

Our results join a growing pharmacoepidemiologic literature on the social and behavioral benefits and harms of

TABLE 4. Long-Term Associations Between ADHD Medication and Substance-Related Events[a]

			Population				Within-Individual			
			Long Term		Concurrent		Long Term		Concurrent	
Cohort	Patients (N)	Substance-Related Events (N)	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Male										
All ADHD patients	581,941	17,637	1.02	0.99–1.06	0.78	0.74–0.81	0.81	0.78–0.85	0.68	0.65–0.72
With no other psychiatric medications	278,570	2,904	0.99	0.91–1.07	0.88	0.80–0.97	0.75	0.67–0.83	0.69	0.60–0.78
With no psychotherapy	357,085	4,996	1.03	0.96–1.10	0.83	0.77–0.89	0.72	0.66–0.78	0.67	0.61–0.74
Incident diagnosis cohort	129,403	3,629	0.93	0.85–1.01	0.88	0.80–0.97	0.82	0.74–0.91	0.76	0.67–0.86
Female										
All ADHD patients	462,820	10,769	1.10	1.05–1.15	0.86	0.82–0.90	0.86	0.82–0.91	0.77	0.72–0.82
With no other psychiatric medications	128,472	897	0.98	0.84–1.14	1.12	0.96–1.30	0.93	0.75–1.14	0.84	0.66–1.06
With no psychotherapy	263,318	2,553	1.12	1.02–1.24	0.97	0.88–1.07	0.83	0.74–0.94	0.79	0.68–0.91
Incident diagnosis cohort	98,190	1,960	0.99	0.88–1.11	0.96	0.86–1.09	0.96	0.83–1.11	0.87	0.74–1.03

[a] Odds ratios test long-term (2-year) and concurrent associations in simultaneous models. Models also control for age and calendar year (population models only) and time since last substance-related event (population and within-individual models). ADHD=attention deficit hyperactivity disorder.

medication treatment for ADHD. This study extended a finding of associations between stimulant medication and lower risk of substance-related problems in Sweden by demonstrating within-individual associations with not only lower concurrent risk but also lower long-term risk of substance-related events (19). Moreover, accumulating findings have also demonstrated within-individual associations with lower risk for injuries, transport accidents, criminality, depression, and suicide (26, 31–36). If these results reflect protective effects, it is possible that differing processes underlie decreased substance-related risk in the short and longer term. For example, concurrent associations may be due to decreased impulsive decision making. In the longer term, accumulating treatment may produce changes in individual behaviors and decisions that aggregate into sustained decreases in substance-related risk, and it is also possible that any benefits result from alterations in prosocial engagement (e.g., as specified by Molina and Pelham [22]). However, the apparently weaker long-term, relative to concurrent, associations suggest that at least some risk reduction may dissipate with time. Research with greater clinical detail should explore these possibilities.

The finding that long-term associations were less clear among female patients relative to male patients may suggest that ADHD medication is associated with less long-term benefit among women. However, our sample was not nationally representative, and differences in associations may reflect characteristics of the included male and female patients. For example, whereas we found more than two male adolescents for every one female adolescent, this sex ratio was reversed among those aged 26 years or older (Table 3). More female ADHD patients received other psychiatric medications and psychotherapy than did male patients (Table 2), raising the possibility that self-referral for comorbid psychiatric problems may have increased the number of included adult female patients (37). Given little prior evidence of sex differences in associations between ADHD medication and substance-related problems (16), further investigation is warranted.

Although these data are national, large, and longitudinal, they are observational. We used multiple design features to attempt to rule out alternative explanations for the observed associations. In particular, within-individual comparisons ruled out all potential confounding factors that were constant within the individual over time (e.g., genetic substance-related liability), and we statistically adjusted for time since prior substance-related events. Sensitivity analyses supported the associations for men and, at least in the short term, for women. At the same time, our analyses could not exclude all time-varying confounding effects. Our concurrent results could be consistent, for example, with the hypothesis that life events prompt some patients to simultaneously decrease their substance involvement and enter psychiatric treatment, thereby producing noncausal medication associations. However, we do not believe that this hypothesis explains the observed long-term associations, and the finding that the associations did not hold for SSRIs may also be evidence that it does not entirely explain our results. Moreover, prior findings of associations with decreased risk of accidents and injuries are arguably less susceptible to this alternative explanation (26, 32–35). Nevertheless, lacking randomization to medication, we cannot rule out all plausible explanations.

Indeed, SSRIs were associated with increased risk of substance-related events in the short term but not in the long term. Although this pattern supports the specificity of the ADHD medication results, it also prompts questions regarding SSRIs. We believe that these associations are unlikely to represent true adverse effects but may rather reflect time-varying confounding by indication. Specifically, initiation of SSRI treatment among ADHD patients may follow the emergence of substance-related problems but still precede some events, producing a spurious positive association.

TABLE 5. Sensitivity Analyses for Long-Term Within-Individual Associations Between ADHD Medication and Substance-Related Events[a]

Sensitivity Analysis	Patients (N)	Substance-Related Events (N)	Long Term		Concurrent	
			Odds Ratio	95% CI	Odds Ratio	95% CI
Male						
Age[b] (2-year interval)						
13–17	258,227	7,439	0.76	0.72–0.81	0.62	0.57–0.66
18–25	141,540	6,508	0.85	0.79–0.91	0.85	0.78–0.94
26–35	53,897	1,051	0.92	0.75–1.13	0.68	0.54–0.87
36–45	54,081	1,072	0.84	0.69–1.02	0.57	0.45–0.72
46+	74,196	1,567	0.87	0.74–1.03	0.62	0.50–0.76
Time interval						
3 years	389,529	11,597	0.79	0.75–0.83	0.69	0.65–0.74
Cumulative duration						
In last 2 years	581,941	17,637	0.80	0.76–0.84	0.72	0.69–0.76
In last 3 years	389,529	11,597	0.79	0.75–0.83	0.74	0.69–0.79
Stimulant medication only						
2-year interval	581,941	17,637	0.83	0.79–0.87	0.68	0.65–0.72
2-year cumulative			0.83	0.79–0.88	0.72	0.68–0.76
Ambulance, inpatient, or emergency events						
2-year interval	581,941	30,300	0.86	0.84–0.89	0.72	0.70–0.75
2-year cumulative			0.89	0.86–0.92	0.75	0.72–0.78
SSRI medication						
2-year interval	581,941	17,637	1.03	0.97–1.10	1.48	1.39–1.56
2-year cumulative			1.20	1.13–1.29	1.42	1.34–1.51
Female						
Age[b] (2-year interval)						
13–17	111,865	2,968	0.80	0.72–0.89	0.83	0.74–0.93
18–25	106,368	3,599	0.92	0.83–1.01	0.94	0.84–1.06
26–35	61,861	922	0.81	0.65–0.99	0.78	0.62–0.99
36–45	74,041	1,362	0.81	0.69–0.96	0.57	0.47–0.69
46+	108,685	1,918	0.93	0.81–1.07	0.53	0.45–0.63
Time interval						
3 years	293,939	6,567	0.84	0.78–0.90	0.80	0.74–0.87
Cumulative duration						
In last 2 years	462,820	10,769	0.92	0.86–0.98	0.78	0.73–0.84
In last 3 years	293,939	6,567	0.89	0.83–0.96	0.82	0.76–0.90
Stimulant medication only						
2-year interval	462,820	10,769	0.90	0.85–0.95	0.76	0.71–0.81
2-year cumulative			0.95	0.89–1.01	0.77	0.72–0.83
Ambulance, inpatient, or emergency events						
2-year interval	462,820	18,458	0.93	0.89–0.97	0.74	0.71–0.78
2-year cumulative			1.08	1.03–1.13	0.73	0.70–0.77
SSRI medication						
2-year interval	462,820	10,769	0.97	0.91–1.04	1.28	1.20–1.37
2-year cumulative			1.15	1.07–1.24	1.25	1.17–1.34

[a] Odds ratios test long-term and concurrent associations in simultaneous models, controlling for time since last substance-related event. Cumulative duration associations reflect differences in odds associated with a 1-year increase in months of medication for attention deficit hyperactivity disorder (ADHD) received in the prior 2 years. SSRI=selective serotonin reuptake inhibitor.
[b] Age group in years at start of long-term follow-up.

Related dynamic treatment-initiation processes have been shown to underlie associations between antidepressant treatment and suicidal behavior (38), and this pattern highlights how selection processes can differ across types of medication. Consequently, whereas the SSRI results may strengthen conclusions from this study, they highlight how such negative controls should not necessarily be viewed as definitively ruling out all alternative hypotheses.

Several additional limitations have implications for future research. First, medication treatment in these data was mostly with stimulants. It will be valuable to examine nonstimulant treatments (including extended-release clonidine and guanfacine) and stimulant types more closely (15). Future studies should also consider dosage and polypharmacy effects. Second, we were able to examine adolescents and adults, but because of the limited follow-up, these data were

not ideally suited to examining earlier childhood treatment. Given studies showing lower substance-related risk among earlier treatment initiators (20), research should examine long-term associations following childhood medication receipt. Third, although there is little existing evidence of substance-specific medication associations (19), future studies should examine whether associations differ across classes of substances (e.g., alcohol, illicit substances). Fourth, we do not know whether our results would generalize to patients without commercial health insurance. Finally, our conclusions are constrained by the limitations of claims data, including undiagnosed conditions, medications taken outside of recorded prescriptions, and, notably, prescriptions filled but not taken. As a consequence, our analyses should be interpreted as analogous to "intent-to-treat" analyses in clinical trials. It is also possible, given the size of the databases, that individuals who switched MarketScan-covered employers were included as multiple enrollee observations.

In conclusion, in a large sample of commercially insured adolescent and adult ADHD patients, ADHD medication was associated with lower concurrent risk and, at least among male patients, lower long-term risk of substance-related events. Given mixed results from clinical trials (39), our results should not be interpreted as supporting the use of ADHD medication in the treatment of substance-related problems. More broadly, our results cannot speak to the possibility of diversion or misuse of stimulants outside of treatment. However, they do join a growing evidence base of protective associations for patients receiving medication therapy. It may be useful to consider these associations in conjunction with other potential benefits and harms (e.g., growth delay) when making treatment decisions (40).

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