Supplemental Materials

SUPPLEMENTAL METHOD

Sub-Cohorts

In addition to our primary analytic sample, we analyzed three sub-samples of ADHD patients. First, we identified ADHD patients who never received other psychiatric medications. Specifically, we excluded patients who ever received antidepressants, anxiolytics (benzodiazepines or buspirone), antipsychotics, medications used in substance use disorder treatment, anti-epileptic medications and/or mood stabilizers, or alpha agonist medications used in ADHD treatment (i.e., clonidine or guanfacine).

Second, we identified ADHD patients who never received psychotherapy (for any diagnosis code). We excluded patients with any inpatient or outpatient claims with the following Current Procedural Terminology (CPT4) psychotherapy codes: 90804, 90816, 90806, 90818, 90808, 90821, 90845, 90846, 90847, 90849, 90853, 90832, 90834, and 90837.

Third, we created an incident ADHD diagnosis cohort (1). This cohort permitted evaluation of associations among patients who were new to ADHD treatment. We required these patients to have at least 12 continuous months of enrollment prior to the month of their first ADHD diagnosis, as well as 365 days without any filled prescriptions for ADHD medication prior to the index diagnosis. Because we included in follow-up only those 2005-2014 enrollment years in which patients were at least 13 years old, note that these patients were no younger than 4 years old at their first ADHD diagnosis, which reduces the possibility of misdiagnosis or treatment outside of clinical guidelines for very young patients (2).

SSRI Medication

We used selective serotonin reuptake inhibitor (SSRI) prescriptions as a negative control. That is, we replaced ADHD medication exposure with SSRI exposure in our cohort of ADHD

patients in order to test whether any associations were specific to ADHD medication or would generalize to SSRIs. Finding that SSRI associations were null or differed from associations with ADHD medication would support the specificity of the association, whereas finding comparable or stronger SSRI associations would suggest that ADHD medication associations merely reflected general effects associated with entering any treatment. We selected SSRIs because they are commonly prescribed and have been used as negative controls in prior studies of ADHD medication (3).

Included SSRIs were identified using national drug codes for the following generic names: *citalopram hydrobromide*, *escitalopram oxalate*, *fluoxetine hydrochloride*, *fluvoxamine maleate*, *paroxetine hydrochloride*, *paroxetine mesylate*, and *sertraline hydrochloride*. Of the included ADHD patients, 20.9% of male patients and 34.4% of female patients received SSRI medication for at least one month of follow-up.

Substance-Related Events

Our analytic approach examined change over time in risk of substance-related problems and required a time-sensitive outcome operationalization. We therefore included as substance-related events only those claims in which (a) the patient received any substance use disorder diagnosis (ICD-9 codes 291.xx, 292.xx, 303.xx, 304.xx, and 305.xx, except tobacco use disorder [305.1]) and (b) the service sub-category indicated that the encounter occurred in an emergency room or department (service sub-category code ending in ‘20’). In order to test whether our results were unduly influenced by this operationalization, we repeated analyses using a broader substance-related event criterion of emergency, ambulance (place of service codes ‘41’ and ‘42’), or inpatient claims.

We coded substance-related events dichotomously on a monthly basis, with months with at least one claim coded as having had an event and months with no claims coded as having no events. Thus, patients could have multiple events included in the analyses during follow-up overall but could only count one event per month. This approach reduced the likelihood that repeated claims resulting from the same substance-related event would be counted as multiple distinct events. When substance-related events occurred during the months in which patients began prescriptions, those months were considered un-medicated if the first event occurred before or on the same date as the first prescription fill.

REFERENCES

1. Schneeweiss S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. Pharmacoepidemiol Drug Saf. 2010;19(8):858-68.

2. Subcommittee on Attention-Deficit/Hyperactivity Disorder: Steering Committee on Quality Improvement and Management. ADHD: Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2011;128(5):1007-22.

3. Lichtenstein P, Halldner L, Zetterqvist J, Sjölander A, Serlachius E, Fazel S, et al. Medication for attention deficit–hyperactivity disorder and criminality. N Engl J Med. 2012;367(21):2006-14.

Table S1

Between-Individuals Risk of Any Substance Use Disorder Diagnosis

ADHD Patients vs. Controls	ADHD Patients			Non-ADHD Controls			OR	(95% CI)
	Overall n	n with SUD	% with SUD	Overall n	n with SUD	% with SUD		
Male	1,579,683	135,415	8.6	1,579,683	44,758	2.8	3.30	(3.26-3.33)
Female	1,414,170	93,034	6.6	1,414,170	25,112	1.8	3.96	(3.90-4.02)

Medicated vs. Never Medicated	Medicated at Least Once			Never Medicated			OR	(95% CI)
	Overall n	n with SUD	% with SUD	Overall n	n with SUD	% with SUD		
Male	1,358,770	111,976	8.2	220,913	23,439	10.6	0.75	(0.74-0.76)
Female	1,253,602	81,623	6.5	160,568	11,411	7.1	0.89	(0.88-0.91)

Note. Risk of any 2005 or onward inpatient or outpatient claim with an ICD-9 SUD diagnostic code. Non-ADHD controls were enrollees who never received an ADHD diagnosis or medication matched, where possible, 1:1 to cases on calendar year and age at first enrollment, sex, and months of enrollment in MarketScan (more than 99.9% of cases could be matched). Medicated group had at least one prescription claim for ADHD medication at any point from 2005 onward, whereas never medicated group had no record of any ADHD medication from 2005 onward. Medicated vs. never medicated odds ratios (ORs) control for age and year of first enrollment and months of enrollment. ADHD = attention-deficit/hyperactivity disorder. SUD = substance use disorder.

Table S2

All Covariate Parameter Estimates from Concurrent Association Models

Variable	Male				Female			
	Population		Within-Individual		Population		Within-Individual	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
ADHD medication	0.81	(0.79-0.83)	0.65	(0.64-0.67)	0.89	(0.87-0.92)	0.69	(0.67-0.71)
Time since last event								
>12 months or none	0.08	(0.08-0.08)	3.77	(3.60-3.94)	0.06	(0.06-0.07)	3.99	(3.78-4.21)
7-12 months (reference)	1		1		1		1	
4-6 months	1.52	(1.44-1.61)	1.02	(0.96-1.08)	1.51	(1.40-1.62)	1.00	(0.94-1.08)
0-3 months	3.44	(3.25-3.65)	1.53	(1.46-1.61)	3.22	(3.01-3.45)	1.46	(1.38-1.56)
Age in years				--				--
13-17	0.95	(0.90-0.99)			1.17	(1.12-1.23)		
18-25	1.98	(1.88-2.08)			2.02	(1.93-2.11)		
26-35	1.36	(1.29-1.44)			1.30	(1.24-1.37)		
36-45	1.09	(1.02-1.16)			1.15	(1.09-1.21)		
>45 (reference)	1				1			
Calendar year				--				--
2005 (reference)	1				1			
2006	1.01	(0.92-1.11)			1.08	(0.96-1.20)		
2007	1.05	(0.96-1.16)			1.20	(1.07-1.34)		
2008	1.05	(0.96-1.15)			1.16	(1.04-1.29)		
2009	1.30	(1.19-1.41)			1.45	(1.31-1.60)		
2010	1.42	(1.31-1.55)			1.51	(1.37-1.67)		
2011	1.59	(1.46-1.72)			1.59	(1.44-1.75)		
2012	1.62	(1.50-1.76)			1.66	(1.50-1.83)		
2013	1.55	(1.43-1.68)			1.60	(1.45-1.77)		
2014	1.55	(1.43-1.68)			1.63	(1.48-1.80)		

Note. ORs estimate concurrent associations with substance-related events among all ADHD patients. Within-individual models control for time since last event only. ADHD = attention-deficit/hyperactivity disorder. OR = odds ratio.

Table S3

Unadjusted Long-Term Within-Individual Associations

Cohort	Long-Term		Concurrent	
	OR	**(95% CI)**	**OR**	**(95% CI)**
	Male			
All ADHD patients	0.88	(0.84-0.92)	0.76	(0.72-0.80)
With no other psychiatric medications	0.88	(0.79-0.98)	0.76	(0.67-0.86)
With no psychotherapy	0.84	(0.78-0.91)	0.79	(0.71-0.87)
Incident diagnosis cohort	0.86	(0.78-0.96)	0.84	(0.74-0.95)
	Female			
All ADHD patients	0.94	(0.89-1.00)	0.84	(0.79-0.89)
With no other psychiatric medications	1.02	(0.84-1.25)	0.87	(0.68-1.09)
With no psychotherapy	0.97	(0.86-1.09)	0.90	(0.79-1.03)
Incident diagnosis cohort	1.02	(0.88-1.17)	0.91	(0.77-1.07)

Note. ORs estimate long-term (two-year) and concurrent associations with substance-related events among all ADHD patients in simultaneous models without time-since-last-substance-related-event covariate. ADHD = attention-deficit/hyperactivity disorder. OR = odds ratio.