ORIGINAL ARTICLE

Psychosis with Methylphenidate or Amphetamine in Patients with ADHD

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ABSTRACT

BACKGROUND

The prescription use of the stimulants methylphenidate and amphetamine for the treatment of attention deficit–hyperactivity disorder (ADHD) has been increasing. In 2007, the Food and Drug Administration mandated changes to drug labels for stimulants on the basis of findings of new-onset psychosis. Whether the risk of psychosis in adolescents and young adults with ADHD differs among various stimulants has not been extensively studied.

METHODS

We used data from two commercial insurance claims databases to assess patients 13 to 25 years of age who had received a diagnosis of ADHD and who started taking methylphenidate or amphetamine between January 1, 2004, and September 30, 2015. The outcome was a new diagnosis of psychosis for which an antipsychotic medication was prescribed during the first 60 days after the date of the onset of psychosis. To estimate hazard ratios for psychosis, we used propensity scores to match patients who received methylphenidate with patients who received amphetamine in each database, compared the incidence of psychosis between the two stimulant groups, and then pooled the results across the two databases.

RESULTS

We assessed 337,919 adolescents and young adults who received a prescription for a stimulant for ADHD. The study population consisted of 221,846 patients with 143,286 person-years of follow up; 110,923 patients taking methylphenidate were matched with 110,923 patients taking amphetamines. There were 343 episodes of psychosis (with an episode defined as a new diagnosis code for psychosis and a prescription for an antipsychotic medication) in the matched populations (2.4 per 1000 person-years): 106 episodes (0.10%) in the methylphenidate group and 237 episodes (0.21%) in the amphetamine group (hazard ratio with amphetamine use, 1.65; 95% confidence interval, 1.31 to 2.09).

CONCLUSIONS

Among adolescents and young adults with ADHD who were receiving prescription stimulants, new-onset psychosis occurred in approximately 1 in 660 patients. Amphetamine use was associated with a greater risk of psychosis than methylphenidate. (Funded by the National Institute of Mental Health and others.)

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Stimulants are effective for the treatment of attention deficit–hyperactivity disorder (ADHD).[1] The prescription of stimulants for the treatment of ADHD is increasing, with the greatest increase occurring among adolescents and young adults.[2,3] According to guidelines for the management of ADHD, the most effective treatments are methylphenidate and amphetamine, with no specification of preference for one over the other.[4] Although amphetamine is used for ADHD treatment in the United States, it is rarely used in other developed countries.[5,6] In 2007, on the basis of results from small preapproval trials that showed a total of 11 patients with symptoms of psychosis, with 743 total person-years of follow-up,[7] the Food and Drug Administration required manufacturers of stimulants to add a warning to drug labels that "stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history."

Both methylphenidate and amphetamine induce the release of dopamine from neurons and inhibit the dopamine transporter, which promotes reuptake of dopamine into presynaptic terminals.[8] However, dopamine release is four times as high with amphetamine as with methylphenidate,[9] whereas methylphenidate is a more potent inhibitor of dopamine transporters.[10] The changes in neurotransmission observed in primary psychosis are more consistent with those induced by amphetamine than methylphenidate. Patients with primary psychotic disorders have higher presynaptic dopaminergic capacity (an index of dopamine release) than controls,[11,12] but no difference in dopamine transporter availability has been detected between patients with schizophrenia and controls.[11] On the basis of similarities between idiopathic psychosis and the effects of amphetamine, we hypothesized that amphetamine use would be associated with a higher risk of psychosis than methylphenidate in adolescents and young adults with ADHD.

Methods

Data Sources

In this cohort study, we used administrative claims databases from two U.S. health care organizations with national coverage, Optum Clinformatics and IBM MarketScan. The Clinformatics database consists of medical and pharmacy claims for patients with United Healthcare insurance, with data available for 68 million patients. MarketScan is a similar source for claims from large employers and insurance plans, with data available for 185 million patients. The study used deidentified data and was approved by the institutional review board of Partners HealthCare. Data licensing agreements allowed Partners HealthCare to use the Optum and IBM databases.

Study Population

Eligible patients were 13 to 25 years of age at entry into the cohort, had had one or more outpatient encounters with a diagnosis of ADHD (defined on the basis of *International Classification of Diseases, 9th Revision* [ICD-9], code 314), and started taking amphetamine or methylphenidate between January 1, 2004, and September 30, 2015. One year of continuous enrollment in medical and prescription drug services before stimulant use was required. The cohort entry date was defined as the date that the stimulant was first dispensed. To eliminate current users and facilitate detection of new-onset psychosis related to treatment, we defined incident use as a new prescription for methylphenidate or amphetamine, with no previous prescription claims for those drugs during the 12 months before cohort entry.[13] We excluded patients with unspecified psychosis, hallucinations, delusional disorder, schizophrenia spectrum disorders, drug-induced psychoses, mood disorders with psychotic features, bipolar disorder, central nervous system disease, or narcolepsy. We also excluded patients who were receiving mood stabilizers, antipsychotic medication, or stimulants not typically used for ADHD (phentermine, pemoline, or methamphetamine) during the 12 months before entry into the cohort. Patients who received a prescription for oral glucocorticoids in the 60 days before entry into the cohort were also excluded because of the potential association of these drugs with psychosis (Fig. 1).[14]

The amphetamine group included patients who began receiving amphetamine–dextroamphetamine, dextroamphetamine, or lisdexamfetamine (a prodrug of dextroamphetamine). The methylphenidate group included patients who began receiving methylphenidate or dexmethylphenidate (the *d-threo*-enantiomer of methylphenidate).

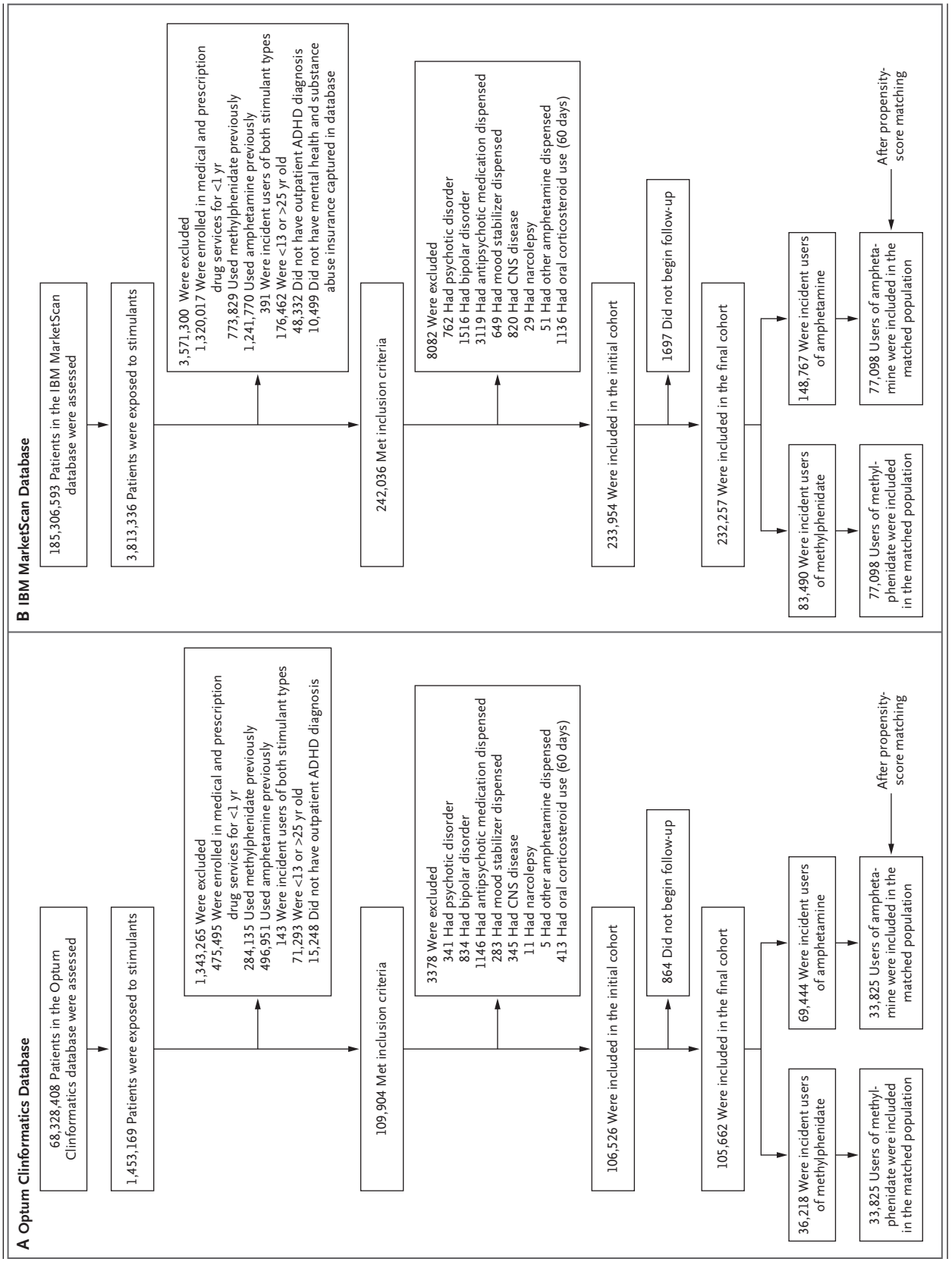

Figure 1 (facing page). Study Cohorts.
Incident users of methylphenidate or amphetamine were defined as patients who received a new prescription for one of these drugs, with no previous prescription claims for the stimulant during the 12 months before cohort entry. ADHD denotes attention deficit–hyperactivity disorder, and CNS central nervous system.

Follow-up started 7 days after the date of the initial dispensation of a stimulant drug, because we assumed that psychosis that resulted in antipsychotic treatment within 1 week after a patient started a stimulant was unlikely to be caused by exposure to the medication, since events during the first 7 days are transient and resolve without the need for an antipsychotic medication.[15] Data for participants were censored at the time of occurrence of psychosis, discontinuation of the stimulant (defined as 60 days after the end of stimulant treatment), crossover to use of the other stimulant, death, end of enrollment, or end of the study (on December 31, 2016 [15 months after enrollment of the last new patients]), whichever occurred first (Fig. 2).

OUTCOMES

The primary outcome was an ICD-9 or ICD-10 code for a new inpatient or outpatient diagnosis of psychosis and a prescription claim for antipsychotic medication on the same day as the initial diagnosis of psychosis or within 60 days thereafter. The following diagnoses qualified as psychosis: unspecified psychosis, hallucinations, delusional disorder, other stimulant use disorders with psychosis, schizophrenia spectrum disorders, and major depressive disorder or bipolar disorder with psychotic features. (The ICD-9 and ICD-10 codes and the antipsychotic medications used to determine the outcome are provided in Tables S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org.) This definition of psychosis was based on a validation study conducted with the use of data from an external New England electronic health record database (Partners HealthCare Research Patient Data Registry), which yielded a positive predictive value of 93.1%.

We used two strategies for internal validation of the outcome (details of internal and external validation are provided in the Supplementary Appendix). First, we conducted a claims profile review[16,17] in which all claims for medication prescriptions, inpatient hospitalizations, and diagnoses and procedure codes for outpatient visits were ordered by date of service or dispensation of medication. Claims profiles for each patient with a psychotic episode were reviewed by a psychiatrist (who was unaware of the stimulant group) starting with the date the patient began taking the stimulant and ending 180 days after

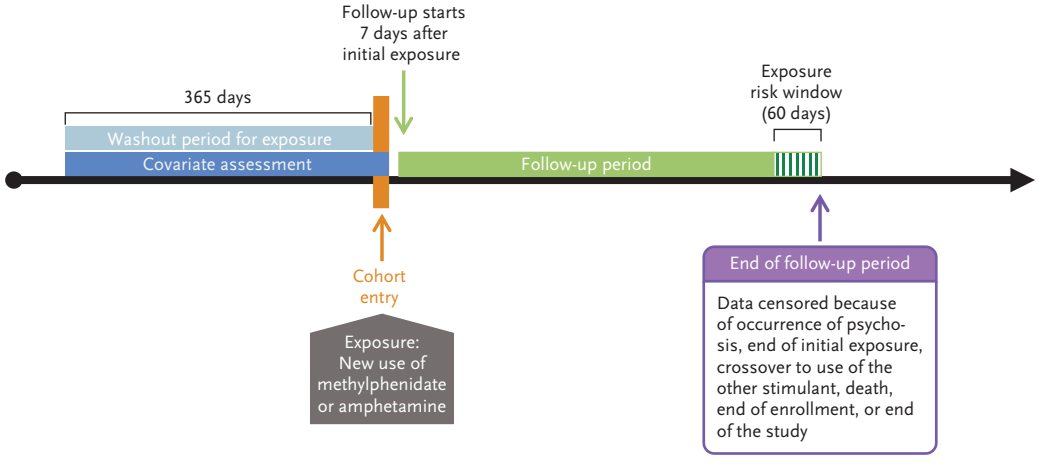

Figure 2. Overview of the Study Design.
The washout period required that patients be enrolled in medical and prescription drug services for 365 days before initial use of a stimulant. Cohort entry is defined as the date of the first prescription claim for methylphenidate or amphetamine.

the initial diagnosis of psychosis to determine whether the medical history was consistent with psychosis. This allowed us to identify patients who had a diagnosis code for psychosis and were treated with an antipsychotic medication but were unlikely to have true psychosis. The positive predictive value for the outcome definition (a diagnosis of psychosis and a prescription for an antipsychotic medication within 60 days after the initial diagnosis of psychosis) from this interval validation study was 91.3% across both databases. The percentage of patients who were unlikely to have had true psychosis was similar in the methylphenidate group and the amphetamine group (10.1% and 8.4%, respectively). Second, we performed analyses that used the following additional stringent outcome definitions of psychosis: prescription of an antipsychotic medication within 30 days rather than 60 days after the initial diagnosis, one inpatient or two outpatient encounters with a diagnosis of psychosis, two inpatient or outpatient encounters with diagnoses of psychosis, and one diagnosis of psychosis and two prescriptions for an antipsychotic medication.

STATISTICAL ANALYSIS

To address potential confounders for the primary prespecified analysis, we used propensity-score matching. Each patient who started receiving methylphenidate was matched in a 1:1 ratio with a patient who started receiving amphetamine. Propensity scores were estimated with the use of logistic-regression models to predict assignment of methylphenidate or amphetamine with the use of all prespecified covariates. The maximum permitted difference in propensity score between matched patients was 1%.[18]

Standardized mean differences were compared before and after propensity-score matching to evaluate how well matching balanced potential confounders for the two stimulant groups.[19] Potential confounders were defined during the 365-day baseline period and included year of cohort entry, age at cohort entry, sex, geographic region, and insurance type. Markers of ADHD severity included the number of outpatient visits for ADHD, emergency department or inpatient hospitalization with a diagnosis of ADHD, treatment with nonstimulant medications, coexisting oppositional–defiant or conduct disorder, and asthma (because previous research has reported increased severity of ADHD symptoms in patients with asthma).[20] We assessed coexisting psychiatric disorders and medications, substance use disorders, provider type, and overall health care utilization (Table S3 in the Supplementary Appendix). These potential confounders were defined according to ICD-9 codes, National Drug Codes, and Current Procedural Terminology procedure codes. For missing data, indicator variables for missing age, sex, region, and insurance type were included in our models. The percentage of patients with missing data for these variables was low (0.002 to 2.400%).

Hazard ratios and 95% confidence intervals were estimated with Cox proportional-hazards models in the matched population in each database. Power analyses showed at least 80% power to detect a 50% higher risk of psychosis with amphetamine than with methylphenidate. Because of the low rate of psychosis, we chose a priori to pool results from the two databases using a fixed-effects meta-analysis. In a secondary analysis, multivariable Cox proportional-hazards outcome models without propensity-score matching were fitted, with adjustment for covariates. Analysis of Schoenfeld residuals showed no violations of the proportional-hazards assumption.

We conducted additional prespecified sensitivity analyses. We extended the exposure risk window to 90 days after stimulant discontinuation. To reduce potential bias from differential follow-up times between stimulant groups, we limited the maximal follow-up to 100 days. To account for potential overlap between the databases, we adjusted 95% confidence intervals to assume 10%, 20%, or 40% overlap.

Post hoc analyses included starting follow-up 1 day instead of 7 days after initial exposure to the stimulant; limiting maximal follow-up to 180 and 365 days; decreasing the exposure risk window to 30 days; and following patients for 365 days and assessing them according to the initial stimulant group, regardless of whether they switched to the other stimulant or discontinued the stimulant. We also performed subgroup analyses stratified according to type of provider (family medicine or internal medicine physicians, pediatricians, or psychiatrists) and age (precollege [13 to 17 years of age] or college [18 to

25 years of age]). We evaluated the rate of psychosis in patients who were prescribed only extended-release formulations, lisdexamfetamine as compared with extended-release methylphenidate, and immediate-release formulations.

A higher risk of psychosis with amphetamine than with methylphenidate could be explained by a higher rate of substance use or more severe psychiatric illness among amphetamine users, which would not have been captured in claims data. To account for this possibility, we performed negative control analyses, in which differences between the groups in the outcomes of emergency department visits or inpatient hospitalizations for alcohol use disorder, all other substance use disorders combined, cannabis use disorders, opioid use disorders, and major depressive disorder without psychotic features at 100 days of follow-up served as negative controls. We estimated the difference between stimulant groups in the prevalence of an unmeasured confounder (e.g., cannabis use) that would fully explain a higher risk of psychosis in one group than in the other.[21] Additional sensitivity analyses are described in the Supplementary Appendix. Analyses were performed with the use of the Aetion platform and R software, version 3.2.1.5, which has previously been validated for a range of studies[22,23] and for predicting findings in clinical trials.[24]

RESULTS

PATIENTS

In the two databases combined, there were 337,919 incident users of stimulants with 232,096 person-years of follow-up; the characteristics of these patients are shown in Table S3 in the Supplementary Appendix. The total population of patients who were matched according to propensity score included 221,846 patients with 143,286 person-years of follow-up, with 110,923 patients in each group. All demographic and clinical characteristics were similar in the two groups, as shown by maximal standardized mean differences of 0.02 (Table 1, and Table S3 in the Supplementary Appendix). We found that 3.8 times as many patients received a prescription for amphetamine in 2014 as in 2005; in contrast, 1.6 times as many patients received a prescription for methylphenidate in 2014 as in 2005. Older patients were more likely to receive amphetamine than methylphenidate (Fig. 3). Amphetamine was prescribed for 72.5% of the patients who were treated by family medicine or internal medicine physicians, for 51.6% treated by pediatricians, and for 63.7% treated by psychiatrists (Fig. S1 in the Supplementary Appendix). The median duration of follow-up (the time from initiation of the stimulant drug until data censoring) was longer in the amphetamine group than in the methylphenidate group: 155 days (interquartile range, 82 to 318) as compared with 113 days (interquartile range, 82 to 209) in the Clinformatics database and 162 days (interquartile range, 82 to 339) as compared with 123 days (interquartile range, 82 to 228) in the MarketScan database. The most common reason for data censoring was the end of exposure to the stimulant. Users of methylphenidate were more likely to cross over to the other drug than users of amphetamine; 16,489 of 119,708 patients (13.8%) in the methylphenidate group crossed over to amphetamine, and 12,233 of 218,211 patients (5.6%) in the amphetamine group crossed over to methylphenidate (Table S4 in the Supplementary Appendix).

OUTCOMES

Across both databases, there were 343 episodes of psychosis (with an episode defined as a new diagnosis code for psychosis and a prescription for an antipsychotic medication) among the 221,846 patients in the matched population: 106 episodes (0.10%) among 110,923 patients in the methylphenidate group and 237 episodes (0.21%) among 110,923 patients in the amphetamine group. The median time from dispensation of the first stimulant to the psychotic episode was 128 days (interquartile range, 48 to 333). For the prespecified primary analysis, new use of amphetamine was associated with a higher risk of psychosis than new use of methylphenidate among patients in the matched population, with a pooled hazard ratio across both databases of 1.65 (95% confidence interval [CI], 1.31 to 2.09). The incidence rate of psychosis was 1.78 episodes per 1000 person-years of drug exposure in the methylphenidate group and 2.83 episodes per 1000 person-years in the amphetamine group. Results of analyses that used increasingly stringent definitions of psychosis as well as other sensitivity

Table 1. Selected Baseline Characteristics after Propensity-Score Matching.*

Variable	Optum Clinformatics Database			IBM MarketScan Database		
	Methylphenidate (N=33,825)	Amphetamine (N=33,825)	Standardized Mean Difference	Methylphenidate (N=77,098)	Amphetamine (N=77,098)	Standardized Mean Difference
Age — yr	17.0±3.2	17.0±3.1	0.004	17.1±3.2	17.1±3.1	0.001
Sex — no. (%)						
Female	12,681 (37.5)	12,633 (37.3)	0.004	28,737 (37.3)	28,678 (37.2)	0.002
Unknown	5 (<0.1)	6 (<0.1)		0	0	
U.S. region — no. (%)						
Northeast	3,071 (9.1)	3,047 (9.0)		13,326 (17.3)	13,210 (17.1)	
North-central or Midwest	9,890 (29.2)	10,028 (29.6)		23,458 (30.4)	23,582 (30.6)	
South	16,455 (48.6)	16,359 (48.4)	0.017	28,295 (36.7)	28,151 (36.5)	0.010
West	4,378 (12.9)	4,364 (12.9)		11,158 (14.5)	11,257 (14.6)	
Other or unknown	31 (0.1)	27 (0.1)		861 (1.1)	898 (1.2)	
Marker of ADHD severity						
No. of outpatient ADHD visits	2.2±3.5	2.2±5.0	0.001	2.2±4.0	2.2±4.7	0.002
ODD or conduct disorder — no. (%)	1,808 (5.3)	1,804 (5.3)	0.001	3,413 (4.4)	3,434 (4.5)	0.001
Atomoxetine use — no. (%)	2,229 (6.6)	2,238 (6.6)	0.001	4,727 (6.1)	4,775 (6.2)	0.003
Clonidine use — no. (%)	281 (0.8)	314 (0.9)	0.010	781 (1.0)	766 (1.0)	0.002
Guanfacine use — no. (%)	377 (1.1)	399 (1.2)	0.006	1,028 (1.3)	1,028 (1.3)	0.000
Coexisting psychiatric condition or medication use — no. (%)						
Depression	6,394 (18.9)	6,478 (19.2)	0.006	12,307 (16.0)	12,434 (16.1)	0.004
Anxiety or PTSD	4,391 (13.0)	4,405 (13.0)	0.001	8,698 (11.3)	8,673 (11.2)	0.001
Antidepressant use	5,245 (15.5)	5,308 (15.7)	0.005	11,439 (14.8)	11,527 (15.0)	0.003
Benzodiazepine use	1,025 (3.0)	1,066 (3.2)	0.007	2,443 (3.2)	2,437 (3.2)	0.000
Prescription opioid use	4,865 (14.4)	4,875 (14.4)	0.001	10,870 (14.1)	10,809 (14.0)	0.002
Substance use — no. (%)						
Alcohol use disorder	485 (1.4)	507 (1.5)	0.005	859 (1.1)	879 (1.1)	0.002
Cannabis use disorder	478 (1.4)	490 (1.4)	0.003	786 (1.0)	797 (1.0)	0.001
Provider type — no. (%)						
Family or internal medicine	11,967 (35.4)	11,864 (35.1)	0.006	28,439 (36.9)	28,284 (36.7)	0.004
Pediatrician	11,589 (34.3)	11,762 (34.8)	0.011	21,753 (28.2)	21,801 (28.3)	0.001
Psychiatrist	7,184 (21.2)	7,204 (21.3)	0.001	13,622 (17.7)	13,715 (17.8)	0.003
No. of prescription claims	6.2±7.2	6.2±7.0	0.004	6.1±7.1	6.1±6.9	0.000

* Plus–minus values are means ±SD. Shown are data after propensity-score matching for a subset of covariates. All covariates were assessed up to 365 days before (and including) the date of cohort entry. A full list of covariates including the data before and after propensity-score matching is provided in Table S3 in the Supplementary Appendix. Percentages may not total 100 because of rounding. ADHD denotes attention deficit–hyperactivity disorder, ODD oppositional–defiant disorder, and PTSD post-traumatic stress disorder.

analyses, including assessment of episodes starting 1 day after drug exposure, were consistent with the results of the primary analysis (Table 2, and Tables S5 through S7 in the Supplementary Appendix). Sensitivity analyses that were restricted to patients without missing data and analyses that used multiple imputation did not change the results meaningfully.

ADDITIONAL ANALYSES

In post hoc analyses, there was a higher risk of psychosis with amphetamine than with methylphenidate among patients treated by family medicine or internal medicine physicians and by pediatricians, but not among those treated by psychiatrists, and the overall effect size was larger among patients of precollege age than among patients of college age (Table 2, and Table S8 in the Supplementary Appendix). We found larger effect sizes when we assessed patients who received only extended-release formulations of either stimulant (hazard ratio for psychosis, 1.77; 95% CI, 1.30 to 2.40) and patients who received lisdexamfetamine as compared with extended-release methylphenidate (hazard ratio, 1.54; 95% CI, 1.10 to 2.16), but a lesser effect size in patients who received immediate-release formulations (hazard ratio, 1.32; 95% CI, 0.77 to 2.29) (Table S9 in the Supplementary Appendix).

In negative control analyses, there were no differences between the two groups in emergency department visits or admissions for substance use disorders for alcohol use (hazard ratio, 1.12; 95% CI, 0.95 to 1.33 [929 events]), other substance use combined (hazard ratio, 1.10; 95% CI, 0.95 to 1.29 [1062 events]), cannabis use (hazard ratio, 1.12; 95% CI, 0.91 to 1.38 [542 events]), or opioid use (hazard ratio, 0.91; 95% CI, 0.63 to 1.33 [228 events]). There was no difference between the stimulant groups in the prevalence of nonpsychotic depression (hazard ratio, 1.03; 95% CI, 0.84 to 1.27 [491 events]). To estimate the effect of unmeasured or underreported confounders, we used cannabis as an example. Using data from the National Survey on Drug Use and Health,[25] we estimated that the prevalence of cannabis use was 35.8% among patients with ADHD. The prevalence of cannabis use among amphetamine users would have to be 97.0% to explain our findings, assuming a relative risk of psychosis of 2.0 with any cannabis use (details are provided in the Supplementary Appendix).[26]

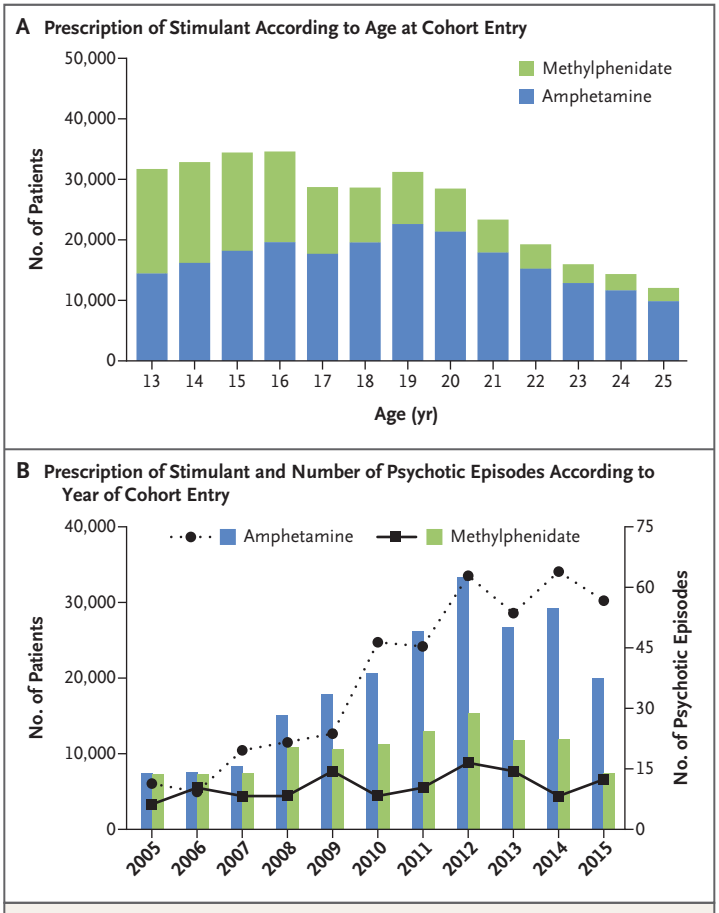

Figure 3. Prescription of Methylphenidate or Amphetamine and Number of Psychotic Episodes According to Age at Cohort Entry and Year of Cohort Entry.

Shown are the combined data from two administrative claims databases (Optum Clinformatics and IBM MarketScan) on the number of patients for whom methylphenidate or amphetamine was prescribed, according to age at cohort entry (Panel A) and year of cohort entry (Panel B). In Panel B, the number of patients who entered the cohort in 2015 is lower than in other years because cohort entry ended on September 30, 2015 (the time of the transition from the 9th revision of the *International Classification of Diseases* to the 10th revision). The bars in Panel B represent the number of patients who started taking a stimulant, according to year of cohort entry; the dotted and solid lines represent the number of psychotic episodes according to year of cohort entry. A psychotic episode was defined as a new diagnosis code for psychosis and a prescription for an antipsychotic medication.

DISCUSSION

In this cohort study involving 221,846 adolescents and young adults with ADHD for whom methylphenidate or amphetamine was prescribed, 343 patients received a diagnosis of psychosis and a subsequent prescription for an antipsychotic medication. The percentage of patients who had a psychotic episode was 0.10% among

Table 2. Psychosis in Patients Initiating Methylphenidate or Amphetamine.*

Variable	Methylphenidate		Amphetamine		Estimated Pooled Hazard Ratio for Psychosis (95% CI)†
	no. of patients	*no. of psychotic episodes (%)*	*no. of patients*	*no. of psychotic episodes (%)*	
Primary analysis					
Unadjusted	119,708	120 (0.10)	218,211	429 (0.20)	1.44 (1.17–1.77)
Adjusted‡	119,708	120 (0.10)	218,211	429 (0.20)	1.55 (1.25–1.92)
Propensity-score matched: PPV 91.3%§	110,923	106 (0.10)	110,923	237 (0.21)	1.65 (1.31–2.09)¶
Sensitivity analyses§					
1 Inpatient or 2 outpatient diagnosis codes for psychosis and prescription for antipsychotic medication: PPV 96.7%	110,923	89 (0.08)	110,923	211 (0.19)	1.75 (1.36–2.25)
2 Inpatient or outpatient diagnosis codes for psychosis and prescription for antipsychotic medication: PPV 98.2%	110,923	71 (0.06)	110,923	163 (0.15)	1.68 (1.26–2.22)
Subgroup analyses†					
Age group					
Precollege age: 13–17 yr	76,767	82 (0.11)	86,505	181 (0.21)	1.62 (1.24–2.12)
College age: 18–25 yr	42,941	38 (0.09)	131,693	248 (0.19)	1.41 (0.99–2.00)
Provider type					
Family or internal medicine physician	41,165	32 (0.08)	108,584	207 (0.19)	1.78 (1.21–2.62)
Pediatrician	38,842	30 (0.08)	41,464	64 (0.15)	1.70 (1.09–2.67)
Psychiatrist	22,349	37 (0.17)	39,201	112 (0.29)	1.38 (0.93–2.04)

* Shown are the data from the Optum Clinformatics and the IBM MarketScan databases combined. The data for each database are provided separately in Tables S5 through S8 in the Supplementary Appendix. The positive predictive values (PPV) for psychosis were derived from an internal validation study that included a claims profile review. A psychotic episode was defined as a new diagnosis code for psychosis and a prescription for an antipsychotic medication.

† The hazard ratios are the pooled estimates across the two databases and were calculated with the use of a fixed-effects meta-analysis of the weighted average of database-specific estimates, weighted by the inverse variance of the estimates.

‡ Analyses that used multivariable models were performed in the full cohort before propensity-score matching and were adjusted according to age at cohort entry; year of cohort entry; sex; region; insurance type; smoking status; the presence of oppositional–defiant disorder or conduct disorder, depression, anxiety, alcohol use disorder, cannabis use disorder, and all other substance use disorders combined; and use of nonstimulant medications, antidepressants, benzodiazepines, and prescription opioids. Provider type was also included in models for the main outcome and age subgroups.

§ Propensity-score matching was used for the primary analysis and for sensitivity analyses, with the use of the full set of covariates listed in Table S3 in the Supplementary Appendix.

¶ The estimated hazard ratio for psychosis in the propensity score–matched population, pooled across the two administrative database cohorts, was prespecified as the primary analysis before unblinding of exposure status.

patients who received methylphenidate and 0.21% among patients who received amphetamine. The incidence of a psychotic episode was 1.78 per 1000 person-years in the methylphenidate group and 2.83 per 1000 person-years in the amphetamine group. This higher rate was consistent in two national health care claims databases.

Post hoc subgroup analyses showed a higher risk of psychosis with amphetamine than with methylphenidate in patients treated by family medicine or internal medicine physicians (the most frequent prescribers) and by pediatricians, with a lower effect size observed in patients treated by psychiatrists; however, the post hoc nature of the analyses and the inadequate power limit the interpretation of these findings.[27] Patients referred to psychiatrists for ADHD may have cognitive deficits or behavioral features that are related to prodromal psychosis, and data on prodromal symptoms would not be

captured in claims data. Psychosis may develop in these patients regardless of stimulant treatment. Alternatively, psychiatrists may prescribe amphetamine more cautiously than other providers and may screen for risk factors for psychosis.

The strengths of this study include the large population size and the consistency of the findings in the two databases. The methods we used to reduce bias, including assessment of incident use of stimulant drugs, outcome validation, and multiple sensitivity analyses, supported our findings.[21,28,29] The attribution of the higher risk of psychosis to amphetamine use was supported by negative control outcome analyses, which showed that there was no difference in the risk of other psychiatric events between the two stimulant groups. The different biologic mechanisms of methylphenidate and amphetamine activity on neurotransmitters could explain our findings.[9-11]

There are several limitations of this study. First, unmeasured confounders such as underreported substance use disorders may have been responsible for our findings. However, in a bias analysis that assessed the potential effects of underreported cannabis use, a difference in the prevalence of cannabis use of 61% between the stimulant groups would have been required to eliminate the effect we found. Second, there may have been cases of stimulant misuse or abuse, since studies report high rates of nonmedical use among college students, with preferential use of immediate-release formulations of amphetamine.[30,31] However, if stimulant misuse among college students was responsible for our findings, we would expect larger effect sizes in college-age patients and in patients who received immediate-release formulations. In contrast, we observed lower effect sizes in these subgroups, which may be because it is possible that these patients would not take stimulants as prescribed because of diversion, less parental supervision, and intermittent use or misuse of the stimulants.[32] Because of the structure of the databases used in the study, we know that the methylphenidate and amphetamine drugs were prescribed and dispensed by an outpatient pharmacy, but we do not know whether or how they were taken by the patients. Diversion among patients who receive a prescription for stimulants is high, ranging from 18.6 to 61.7%, and diversion of amphetamine is greater than diversion of methylphenidate.[33-37] Finally, we had no information on race, ethnic group, or socioeconomic status. Our findings are not generalizable to patients who have public insurance or no insurance, which disproportionately applies to patients who are black or Hispanic.[38]

The absolute rate of psychosis and the difference in the rate of psychosis between the groups exposed to the two drugs was low (difference, approximately 1 per 1000 person-years), possibly because of our stringent outcome definition that led to high specificity of our relative rate estimates. However, this difference may be clinically significant in the context of an exposure with high prevalence. In the databases used for this study, 2 million patients received a prescription for amphetamine, including current users who were excluded from the population. A difference of 1 per 1000 person-years potentially confers additional risk of psychosis with amphetamine in thousands of patients.

In conclusion, the risk of new-onset psychosis was approximately 1 in 660 patients who received a prescription for stimulants for ADHD, but the risk was about twice as high among patients who started amphetamine as among patients who started methylphenidate.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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