Widely Prescribed Stimulants and the Risk of Psychosis in Young People with ADHD

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Disclosures

- No relevant conflicts of interest

Prescription Stimulants

Methylphenidate

- Methylphenidate
- Dexmethylphenidate

Amphetamine

- Amphetamine/ dextroamphetamine
- Dextroamphetamine
- Lisdexamfetamine

*Clinical guidelines for ADHD: methylphenidate and amphetamine medications have similar effect size for treatment of ADHD symptoms

Prevalence of Stimulant Use in U.S.

- **6.1 million** children between ages 4 – 17 (9.4%) ever diagnosed with ADHD (CDC, 2016)
- Amphetamine/dextroamphetamine most commonly abused prescription drug by **high school seniors**
- **16 million adults** used prescription stimulants (not necessarily prescribed) in 2016
  - 5 million misuse

Compton et al., *American Journal of Psychiatry*, 2018

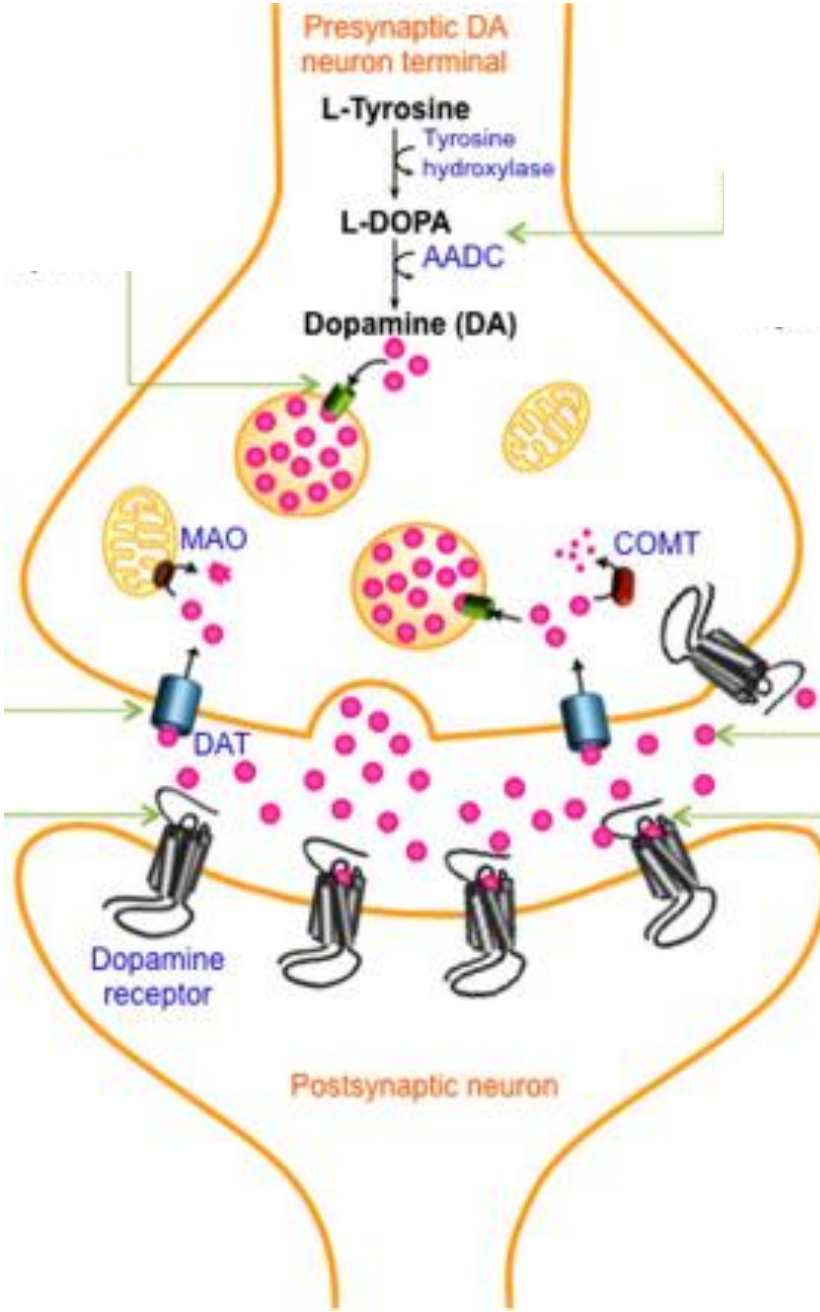
FDA Warning: Prescription Stimulants and Psychosis/Mania

- FDA conducted review of RCT's for prescription stimulants in 2006
  - **11 psychotic events in stimulant arms**
  - **No events in placebo arms**
  - Median trial duration: 23 days
- Warning added to stimulant labels in 2007:
  - "Stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history"
- Despite high prevalence of methylphenidate and amphetamine, no comparative studies of risk of psychosis or mania

Mosholder et al., *Pediatrics* 2009;123:611–616

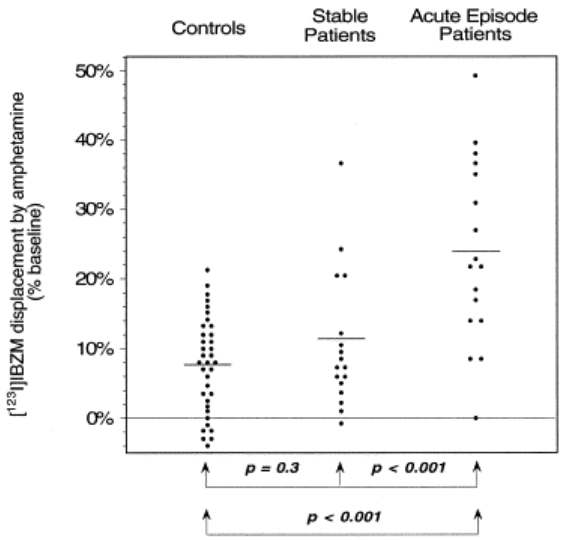
Mechanism of Action of Stimulants

- All stimulants have in common:
  - Inhibition of dopamine transporter (DAT)
  - Increased presynaptic DA release

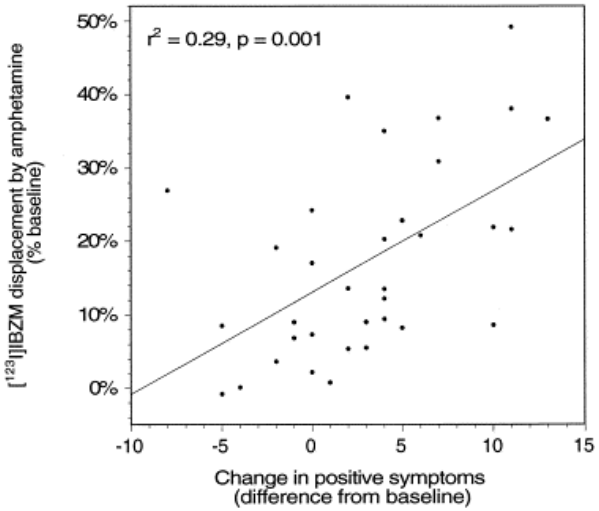


Dopamine and Psychosis

Amphetamine-induced dopamine release



Dopamine and psychotic symptoms



Laruelle M. *Biol Psychiatry* 1999

AGE OF ONSET OF PSYCHOSIS

Age of Onset of Psychosis

- Do patients with premorbid prescription stimulant use have an earlier onset of psychosis?
- 205 patients recruited from McLean Hospital
- Exposure to prescription stimulants prior to onset of psychosis
- SCID-IV diagnosis

	Not exposed (n=123)	**Exposed (n=82)**	**Test statistic**	**p value**
Age	38.1 ± 12.6	28.0 ± 9.5	t=-6.5	<0.001
Gender (M)	74 (60.2%)	62 (75.6%)	X^2=5.3	0.02
Diagnosis: Schizophrenia SAD BPAD MDD NOS	 73 (59.4%) 39 (31.7%) 1 (0.8%) 3 (2.4%) 7 (5.7%)	 37 (45.1%) 34 (41.5%) 2 (2.4%) 0 9 (11.0%)	X^2=7.8	0.10
First-degree relative	17 (13.8%)	6 (7.3%)	X^2=2.1	0.15
Education	13.8 ± 2.4	13.5 ± 2.4	t=0.8	0.41
IQ	108.8 ± 8.4	107.7 ± 9.4	t=0.66	0.51
Cannabis	39 (31.7%)	52 (63.4%)	X^2=20.0	<0.001
Other substance use	20 (16.3%)	22 (26.8%)	X^2=20.0	0.07

Age of Onset of Psychosis

- Patients exposed to prescriptions stimulants had earlier age of onset of psychosis
  - Prescription stimulant use: **-3.1 years** (95% CI -5.3, -0.9)
  - Male gender: **-2.9. years** (95% CI -5.7, -0.1)
  - Cannabis use: **-2.6 years** (95% CI -4.8, 0.3)
  - Family history of psychosis: **-3.8 years** (95% CI -7.1, -0.6)

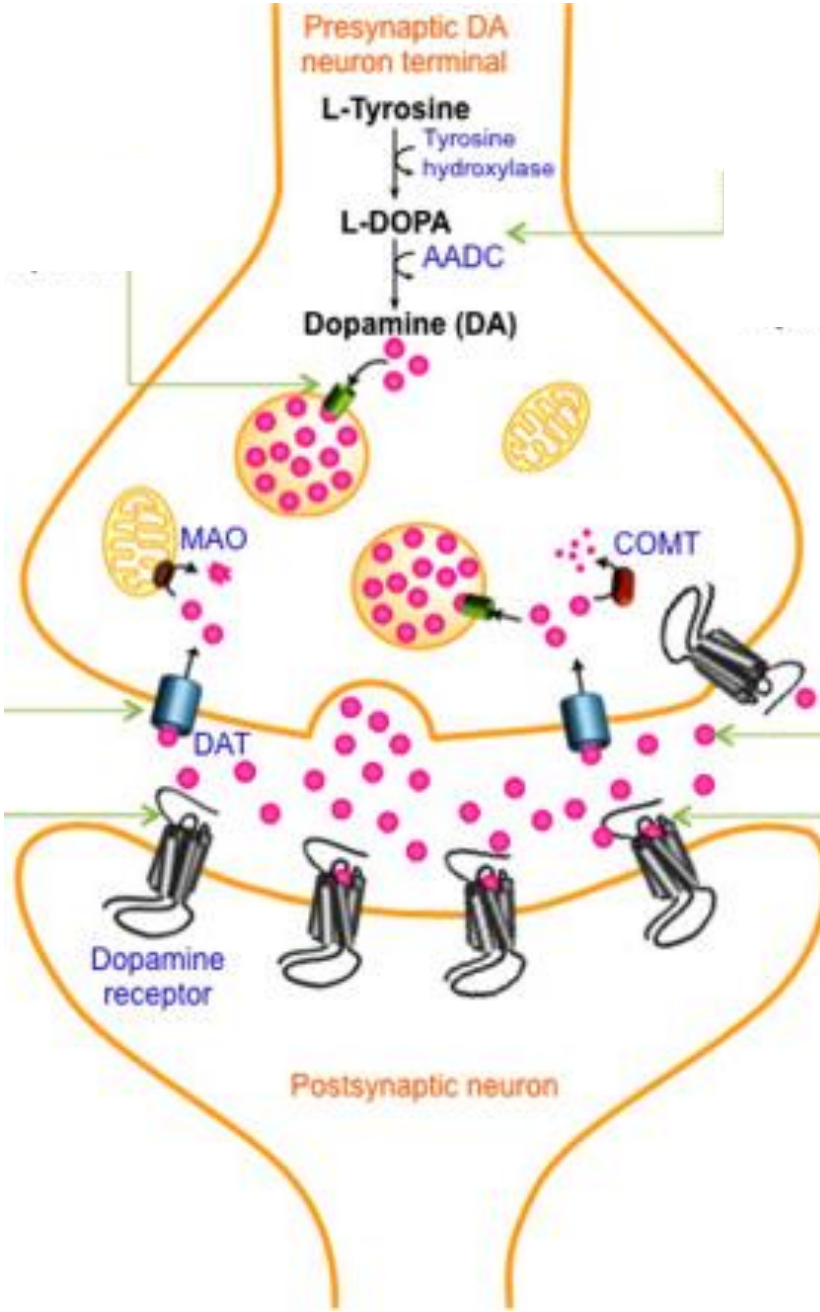
- Cognitive deficits associated with earlier onset of psychosis in existing literature, so perhaps relationship driven by greater cognitive deficits in those prescribed stimulants?
  - Similar IQ in exposed vs. non-exposed
  - IQ was not associated with earlier age of onset

Moran LV et al., *J Psychiatr Res*, 2015, 71: 41-47

RISK OF PSYCHOSIS WITH WIDELY PRESCRIBED STIMULANTS

Mechanism of Action of Stimulants

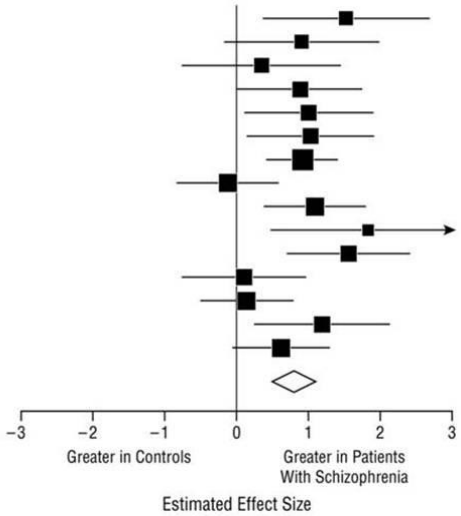
- All stimulants have in common inhibition of dopamine transporter (DAT) and increased presynaptic DA release
- Amphetamine is a “releaser”
  - ↑ striatal release (more pronounced than DAT inhibition)
- Methylphenidate is “blocker”
  - ↑ DAT inhibition (more pronounced than striatal release)



Daberkow et al., *J Neurosci* 2013, 33(2):452-463
Chadchankar et al., *J Pharmacol Exp Ther* 2012 341:484–492.

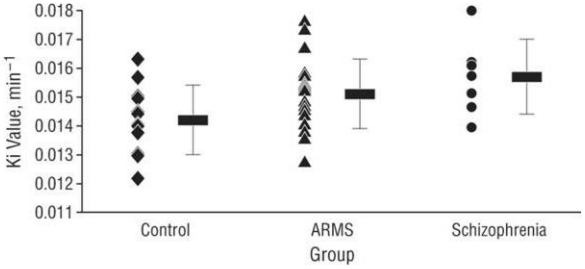
Increased presynaptic dopaminergic capacity (release)

Schizophrenia



Howes O. *Arch Gen Psychiatry* 2012

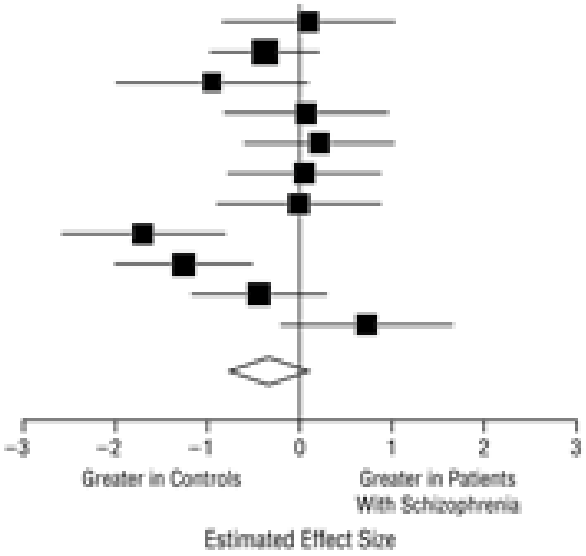
At risk



Howes O. *Arch Gen Psychiatry* 2009

Similar findings in mania with psychotic features

Dopamine Transporter Availability



Howes O. *Arch Gen Psychiatry* 2012

- Meta-analysis showed no significant alteration in dopamine transporter availability

Hypothesis: amphetamine associated with greater risk of psychosis than methylphenidate

	Presynaptic DA release	Dopamine transporter inhibition
Schizophrenia/Psychosis	↑↑↑	-
Stimulants used for ADHD		
Amphetamines	↑↑↑	↑
Methylphenidate	↑	↑↑↑

STUDY DESIGN

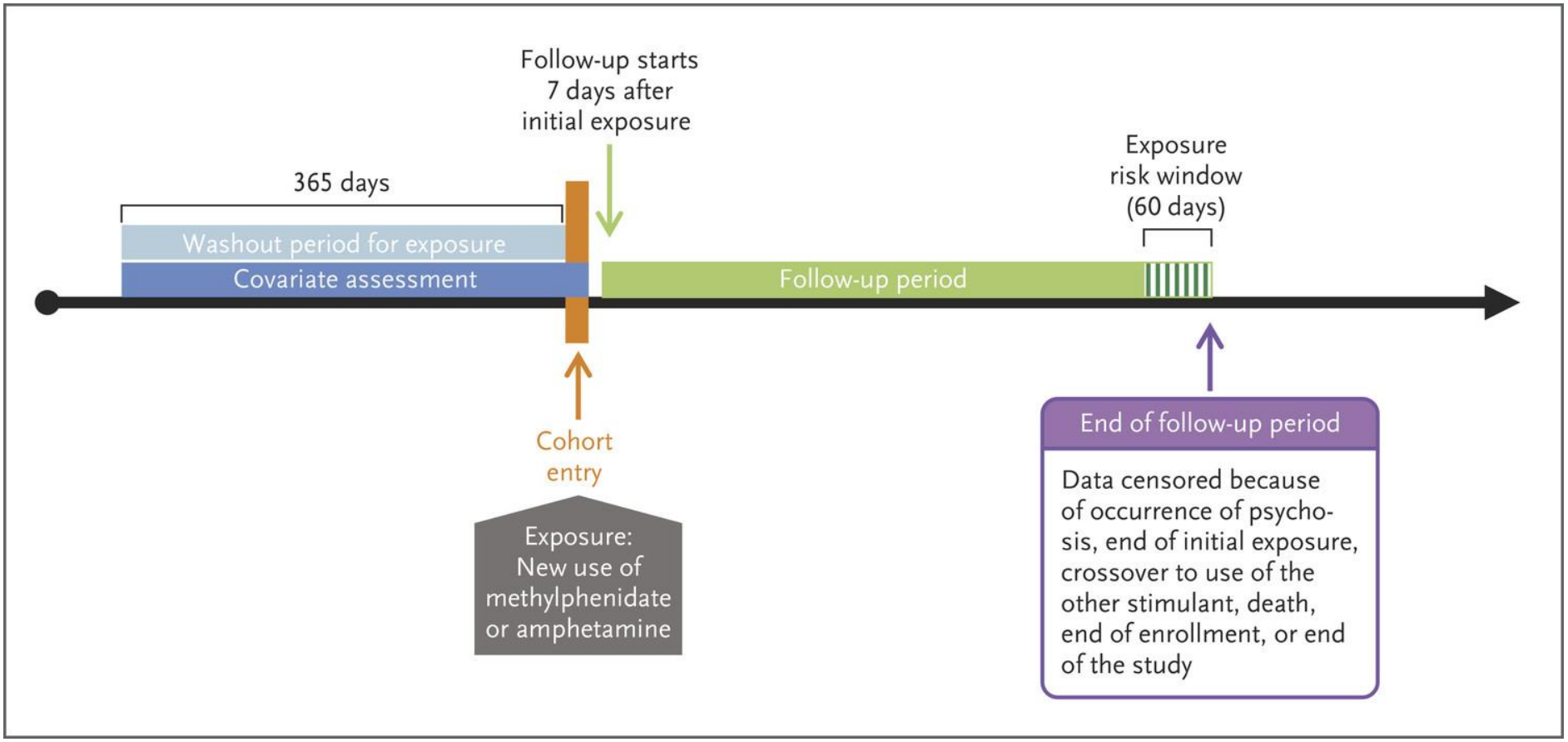
Data Sources: Real World Evidence

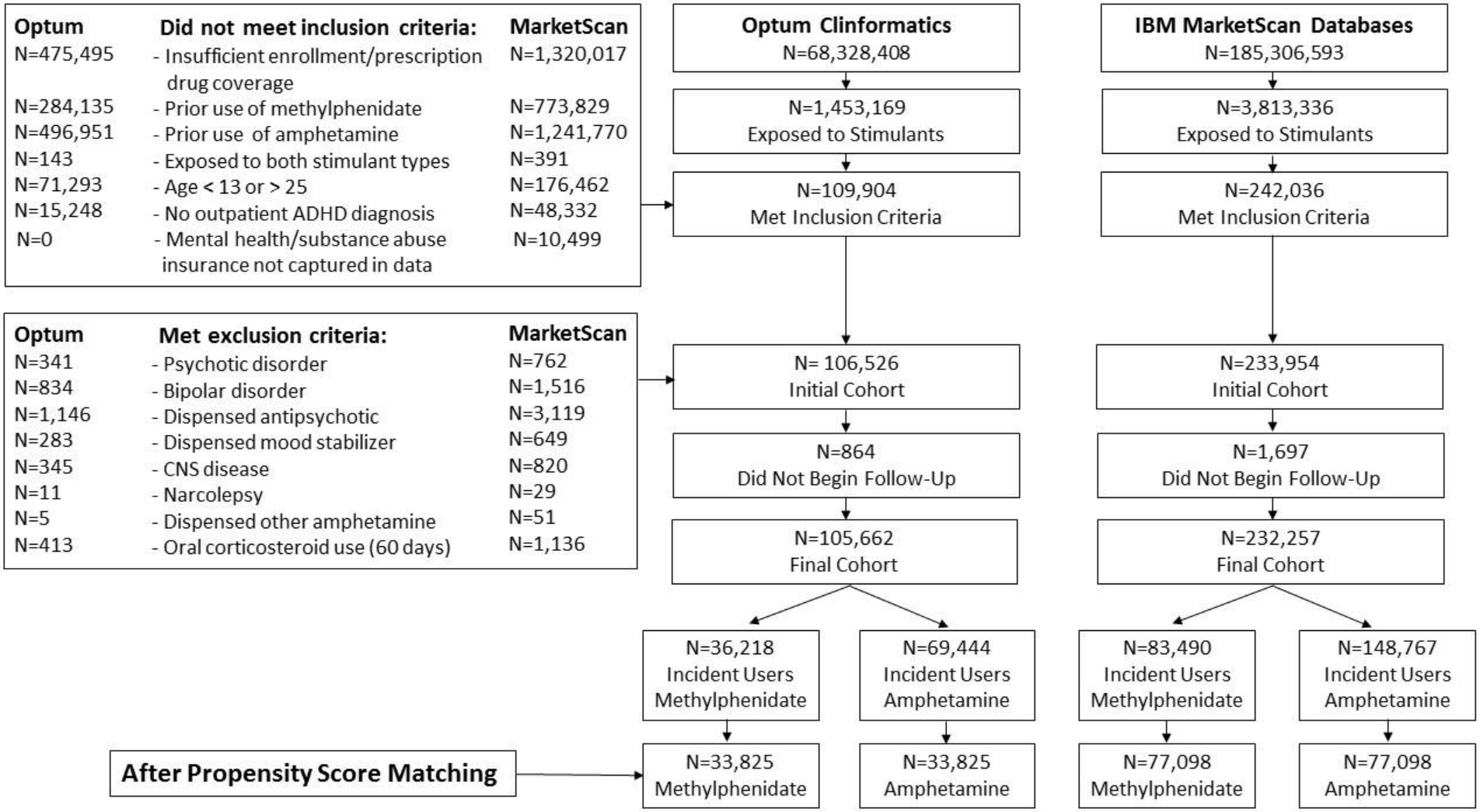
- **Insurance Claims**
  - Dispensed prescription claims is gold standard for measurement of drug exposure
  - Diagnosis: ICD9/ICD10 codes, dates
    - Inpatient, outpatient, ER visits
  - Diagnoses, procedure codes for outpatient and inpatient encounters linked to pharmacy claims data by member ID
- **Optum Clinformatics**
  - 68 million patients
  - United Health
- **IBM MarketScan**
  - 185 million patients
  - Commercial employer-based insurance plans
- Aetion platform
- Incident user, active comparator design

Cohort identification

- **Inclusion Criteria**
  - Patients age 13 – 25 years old
  - ≥ 1 outpatient ADHD encounter
  - No prior use of amphetamine or methylphenidate in past year
  - Continuous enrollment and prescription drug coverage for preceding 365 days
  - Started either amphetamine or methylphenidate between 1/1/2004 (1/1/2005 Optum) and 9/30/2015
- **Exclusion Criteria**
  - Psychosis diagnosis code
  - Bipolar disorder diagnosis code
  - Any antipsychotic or mood stabilizer use
  - CNS disease, narcolepsy
  - Other stimulants: phentermine, pemoline, methamphetamine
  - Oral corticosteroid use in past 60 days
- **Excluded psychosis codes (ICD)**
  - Psychotic disorder unspecified/NOS
  - Psychosis associated with medical conditions
  - Non-organic transient psychoses
  - Hallucinations
  - Delusional disorder
  - Substance-induced psychotic disorders
  - Schizophrenia/Schizophreniform
  - Schizoaffective Disorder
  - Bipolar disorder with psychosis
  - Major depressive disorder with psychosis

Overview of Study Design




Optum
Did not meet inclusion criteria:
MarketScan
N=475,495
- Insufficient enrollment/prescription drug coverage
N=1,320,017
N=284,135
- Prior use of methylphenidate
N=773,829
N=496,951
- Prior use of amphetamine
N=1,241,770
N=143
- Exposed to both stimulant types
N=391
N=71,293
- Age < 13 or > 25
N=176,462
N=15,248
- No outpatient ADHD diagnosis
N=48,332
N=0
- Mental health/substance abuse insurance not captured in data
N=10,499
Optum
Met exclusion criteria:
MarketScan
N=341
- Psychotic disorder
N=762
N=834
- Bipolar disorder
N=1,516
N=1,146
- Dispensed antipsychotic
N=3,119
N=283
- Dispensed mood stabilizer
N=649
N=345
- CNS disease
N=820
N=11
- Narcolepsy
N=29
N=5
- Dispensed other amphetamine
N=51
N=413
- Oral corticosteroid use (60 days)
N=1,136
Optum Clinformatics
N=68,328,408
N=1,453,169
Exposed to Stimulants
N=109,904
Met Inclusion Criteria
N= 106,526
Initial Cohort
N=864
Did Not Begin Follow-Up
N=105,662
Final Cohort
IBM MarketScan Databases
N=185,306,593
N=3,813,336
Exposed to Stimulants
N=242,036
Met Inclusion Criteria
N=233,954
Initial Cohort
N=1,697
Did Not Begin Follow-Up
N=232,257
Final Cohort
N=36,218
Incident Users
Methylphenidate
N=69,444
Incident Users
Amphetamine
N=83,490
Incident Users
Methylphenidate
N=148,767
Incident Users
Amphetamine
After Propensity Score Matching
N=33,825
Methylphenidate
N=33,825
Amphetamine
N=77,098
Methylphenidate
N=77,098
Amphetamine

Primary Analysis

- **Primary Analysis**
  - **Propensity score (PS) matching**: logistic regression model using all pre-defined covariates assigns probability of assignment of **exposure** to amphetamine vs. methylphenidate
  - Cox proportional hazards model in PS matched participants in each database
    - 1:1 PS nearest neighbor matching with 1% maximal matching caliper
    - PS matching performed within each database separately
  - Fixed effects meta-analysis to pool across two databases was pre-specified primary analysis

Covariates for Propensity-Score Matching

- **Demographic**
  - Age at cohort entry
  - Sex
  - Year of cohort entry
  - Region of US (NE, Midwest, S, W)
  - Insurance Type
- **Marker of ADHD Severity**
  - # outpatient ADHD visits
  - Inpatient hospitalization - ADHD
  - ED visits – ADHD
  - Oppositional/conduct disorder
  - Atomoxetine use
  - Guanfacine use
  - Clonidine use
  - Asthma
- **Overall healthcare utilization**
  - # outpatient visits
  - Inpatient, ED visits
  - # prescriptions
  - Total cost of medical services
- **Psychiatric medications**
  - Antidepressants (SSRI, SNRI, TCA, Other)
  - Benzodiazepines
- **Psychiatric comorbidity/severity**
  - Outpatient/inpatient/ED visits
  - Comorbid conditions:
    - Depression
    - Anxiety/PTSD
    - Obsessive compulsive disorder
    - Pervasive developmental/autism
    - Learning disabilities
    - Intellectual delay
    - Personality disorders
      - Schizotypal/schizoid/paranoid
      - Other personality disorders
- **Substance abuse**
  - Detox/rehabilitation procedure codes
  - Inpatient, ED and outpatient SUD visits
  - Nicotine use disorder
  - Alcohol use disorder (Dx or Rx)
  - Cannabis use disorder
  - Cocaine/stimulant use disorder
  - Opioid use disorder (Dx or Rx)
  - Polysubstance/other substance use
  - Proxy: prescription opioids, chronic pain

Outcome: External Validation Study

- **External EHR database: Partners Research Patient Data Registry (RPDR)**
- 1 inpatient/outpatient psychosis code and antipsychotic medication
- 2,718 patients with similar inclusion/ exclusion criteria in RPDR:
  - Followed until single psychotic diagnosis code or end of available data
  - 65 patients with ICD-9/ICD10 psychosis
  - 24 out of 65 patients not psychotic
- Adding antipsychotic medication within 60 days improved accuracy: PPV 93.1%

- **Outcome psychosis codes (ICD9/10)**
  - Psychotic disorder unspecified/NOS
  - Brief psychotic disorder/Non-organic transient psychoses
  - Hallucinations
  - Delusional disorder
  - Other stimulant-induced psychosis
  - Schizophrenia/Schizophreniform
  - Schizoaffective Disorder
  - Bipolar disorder with psychosis
  - Major depressive disorder with psychosis

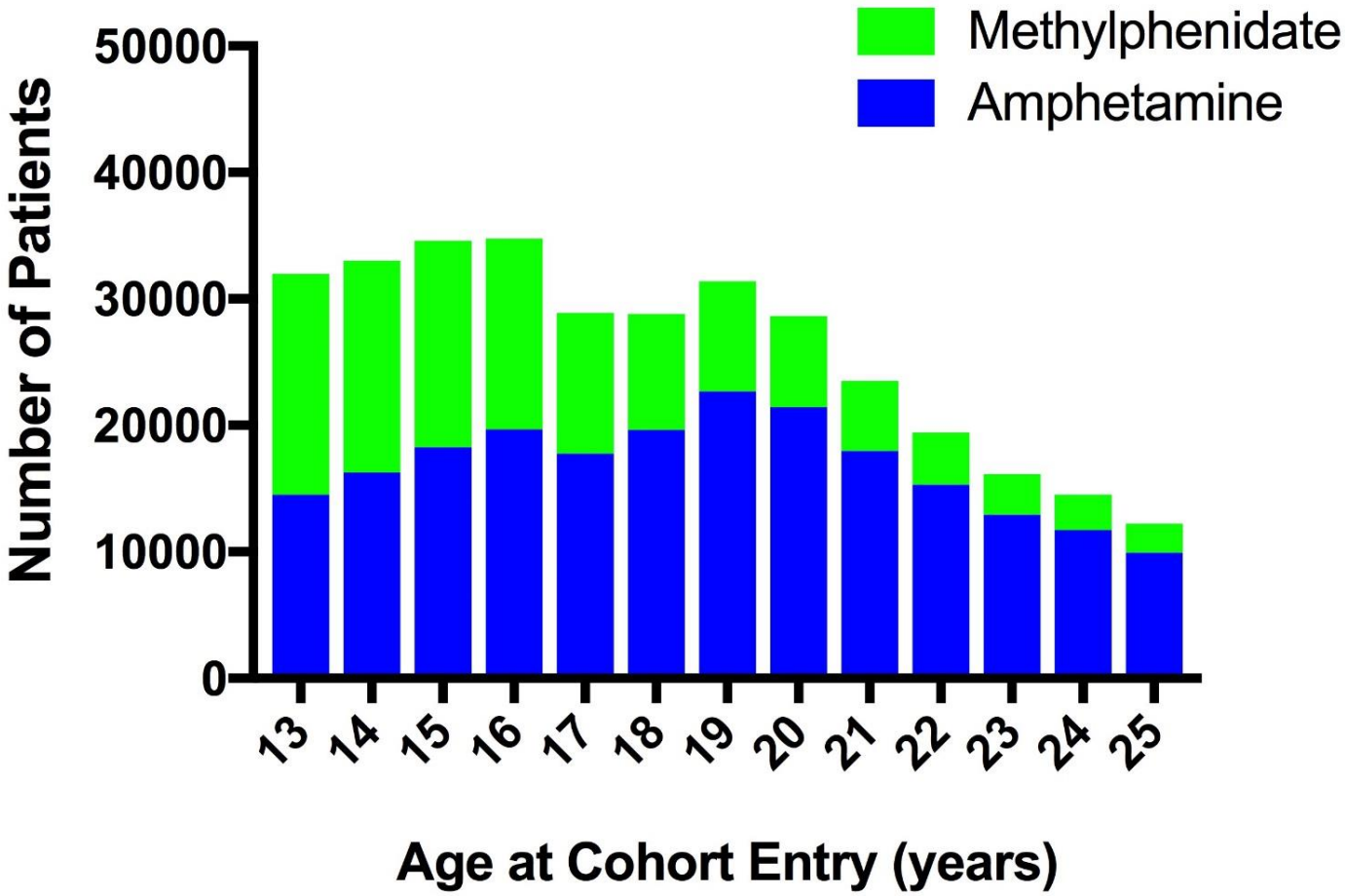
	Psychotic	Not Psychotic	Total	PPV
1 psychosis code +Rx	27	2	29	93.1%
1 psychosis code -Rx	14	22	36	38.9%
Total	41	24	65	

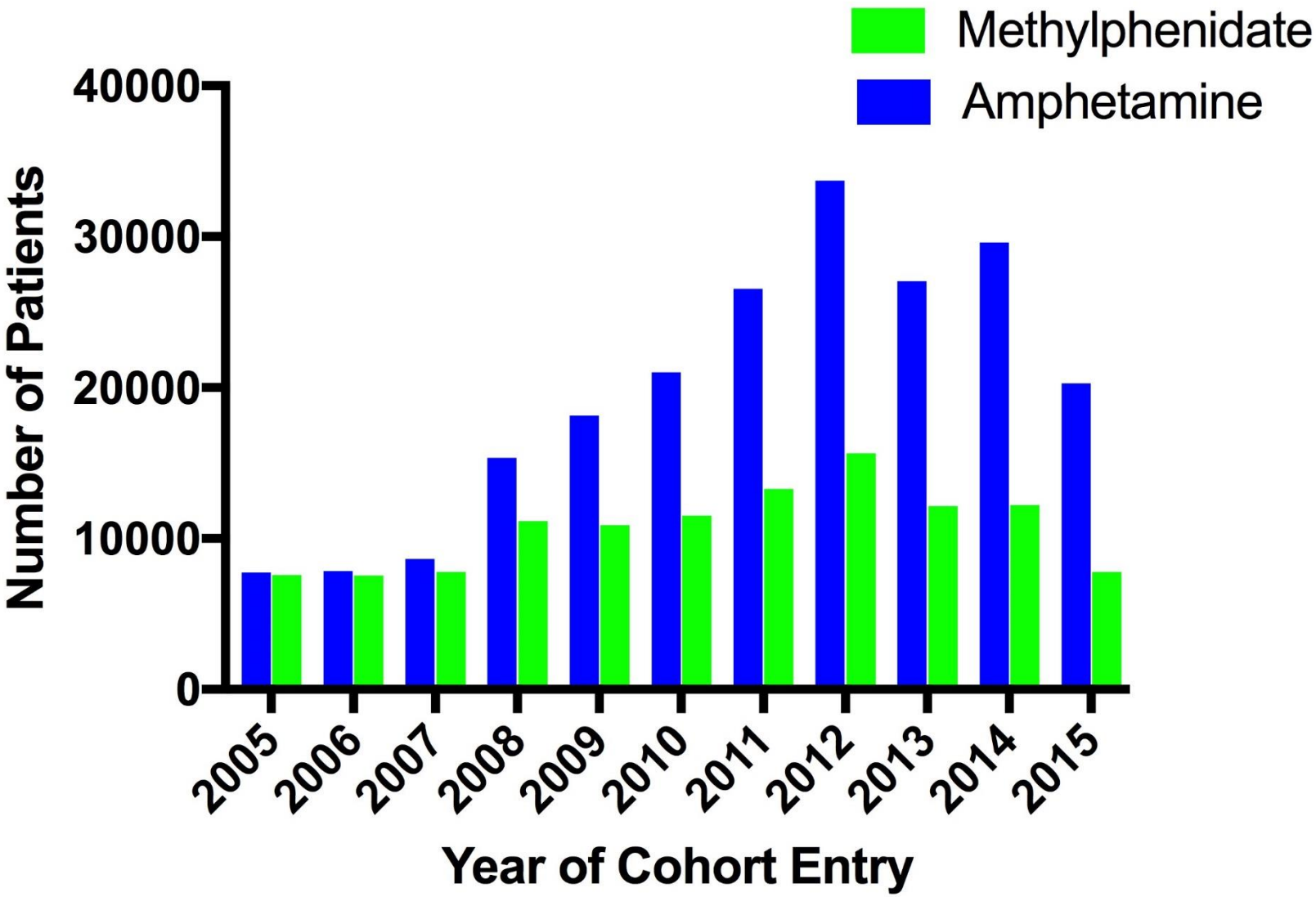
Outcome: Internal Validation Study

- **Claims profile review**
- For all patients who developed outcome (psychosis diagnosis + antipsychotic medication), reviewed claims profile from cohort entry date until 180 days after initial psychosis diagnosis
- Blinded to stimulant group
- PPV 91.3%
- Proportion of patients with false positive rate slightly higher in methylphenidate group
  - 10.0% methylphenidate vs. 8.4% amphetamine

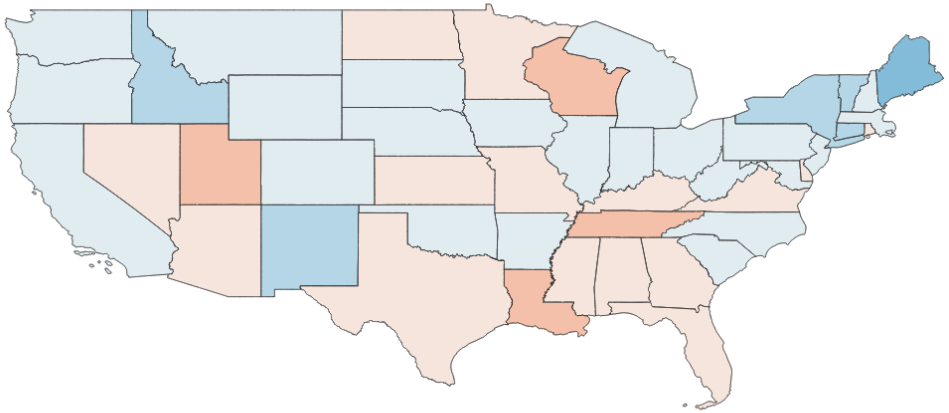
- **Reasons for false positive**
  - Typographical errors (single 295.3 in series of 296.3 codes)
  - Psychosis unlikely to be due to stimulants (alcohol withdrawal delirium, cannabis-induced psychotic disorder)
  - ER diagnosis of psychosis NOS followed by inpatient hospitalization without psychosis diagnosis
  - Single psychosis code, antipsychotic prescribed at different visit associated with non-psychotic diagnosis
  - Inconsistent inpatient codes (primary dx 296.33 MDD without psychotic features + non-primary dx 296.44 BPAD mania with psychotic features)

Stimulant Prescribing Trends in Adolescents and Young Adults

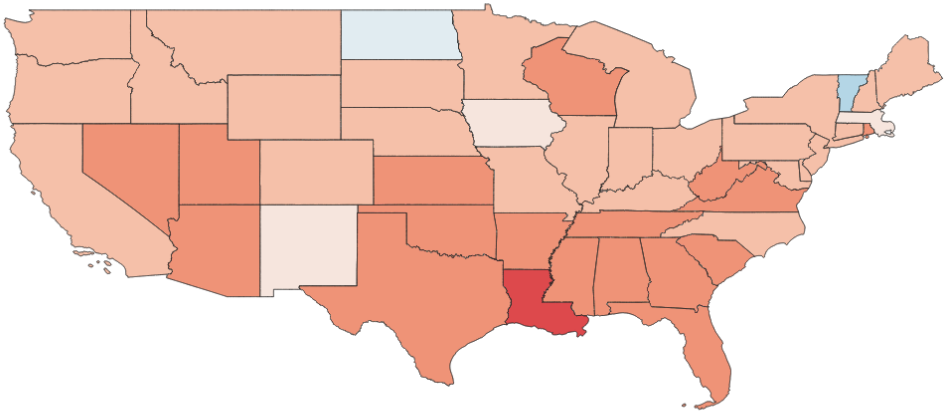

Methylphenidate
Amphetamine
Number of Patients
50000
40000
30000
20000
10000
0
13
14
15
16
17
18
19
20
21
22
23
24
25
Age at Cohort Entry (years)


Methylphenidate
Amphetamine
Number of Patients
40000
30000
20000
10000
0
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
Year of Cohort Entry

Methylphenidate vs. Amphetamine: Prescriber Preferences



2005 - 2006



2013 - 2014

Percent of patients who were who started on methylphenidate (BLUE) versus amphetamine (RED)

Results

	OPTUM CLINFORMATICS After Propensity-Score Matching			MARKETSCAN After Propensity-Score Matching		
	METHYL (N=33,825)	**AMPH** (N=33,825)	**SMD**	**METHYL** (N=77,098)	**AMPH** (N=77,098)	**SMD**
Age	17.0 ± 3.2	17.0 ±3.1	0.04	17.1 ± 3.2	17.1 ± 3.1	0.001
Sex						
Female	12,681 (37.5%)	12,633 (37.3%)	0.004	28,737 (37.3%)	28,678 (37.1%)	0.002
Region						
Northeast	3,071 (9.1%)	3,047 (9.0%)	0.017	13,326 (17.3%)	13,210 (17.1%)	0.010
North Central	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%)		28,295 (36.7%)	28,151 (36.5%)	
West	4,378 (12.9%)	4,364 (12.9%)		11,158 (14.5%)	11,257 (14.6%)	
ADHD Severity						
# outpatient	2.2 ± 3.5	2.2 ±5.0	0.001	2.2 ± 4.0	2.2 ± 4.7	0.002
ODD/Conduct	1,808 (5.3%)	1,804 (5.3%)	0.001	3,413 (4.4%)	3,434 (4.5%)	0.001
Atomoxetine	2,229 (6.6%)	2,238 (6.6%)	0.001	4,727 (6.1%)	4,775 (6.2%)	0.003

	OPTUM CLINFORMATICS After Propensity-Score Matching			MARKETSCAN After Propensity-Score Matching		
	METHYL (N=33,825)	**AMPH** (N=33,825)	**SMD**	**METHYL** (N=77,098)	**AMPH** (N=77,098)	**SMD**
Psychiatric Comorbidity						
Depression	6,394 (18.9%)	6,478 (19.2%)	0.006	12,307 (16.0%)	12,434 (16.1%)	0.004
Anxiety/PTSD	4,391 (13.0%)	4,405 (13.0%)	0.001	8,698 (11.3%)	8,673 (11.2%)	0.001
Antidepressants	5,245 (15.5%)	5,308 (15.7%)	0.005	11,439 (14.8%)	11,527 (15.0%)	0.003
Benzodiazepines	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 abuse						
Alcohol use disorder or Rx	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

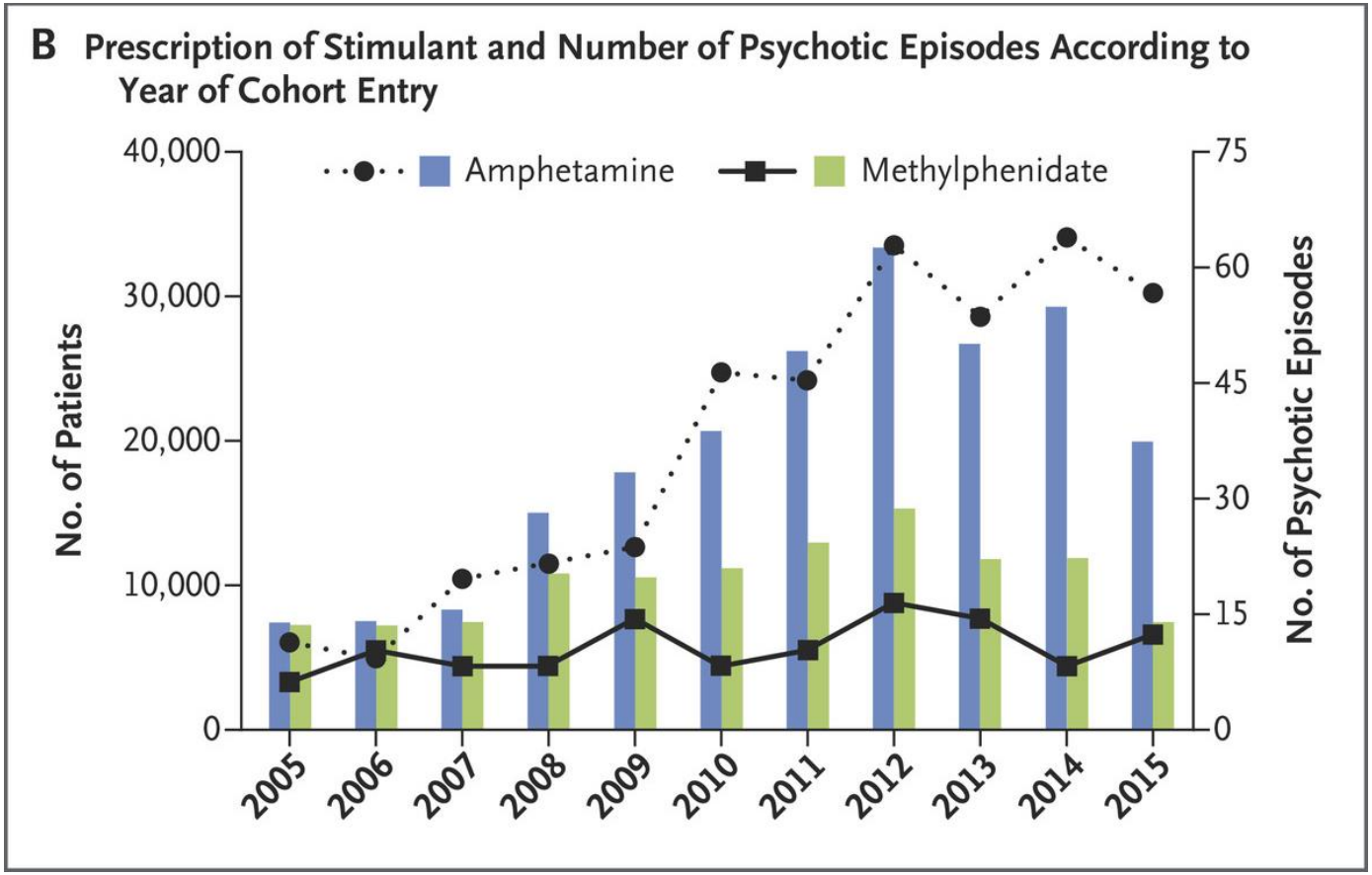
Amphetamine associated with increased risk of psychosis compared with methylphenidate

	Optum Clinformatics					IBM MarketScan					Combined
	METHYL		AMPHET			METHYL		AMPHET			
	N	#	N	#	HR (95% CI)	N	#	N	#	HR (95% CI)	Pooled Estimate HR (95% CI)
Crude	36,218	25	69,444	127	**1.87** (1.22, 2.88)	83,490	95	148,767	302	**1.33** (1.06, 1.68)	**1.44** (1.17, 1.77)
PS Matched	33,825	20	33,825	62	**2.23** (1.34, 3.71)	77,098	86	77,098	175	**1.53** (1.18, 1.98)	**1.65 (1.31, 2.09)**

Moran LV et al., *N Engl J Med*, 2019, 380(12): 1128-38

Sensitivity analyses: More stringent definitions of psychosis

- 1 inpatient OR 2 outpatient + antipsychotic:
  - HR: **1.75** (1.36, 2.25)
  - PPV: 96.7%
- 2 encounters + 2 prescription claims for antipsychotics:
  - HR: **1.78** (1.32, 2.41)
  - PPV: 98.3%



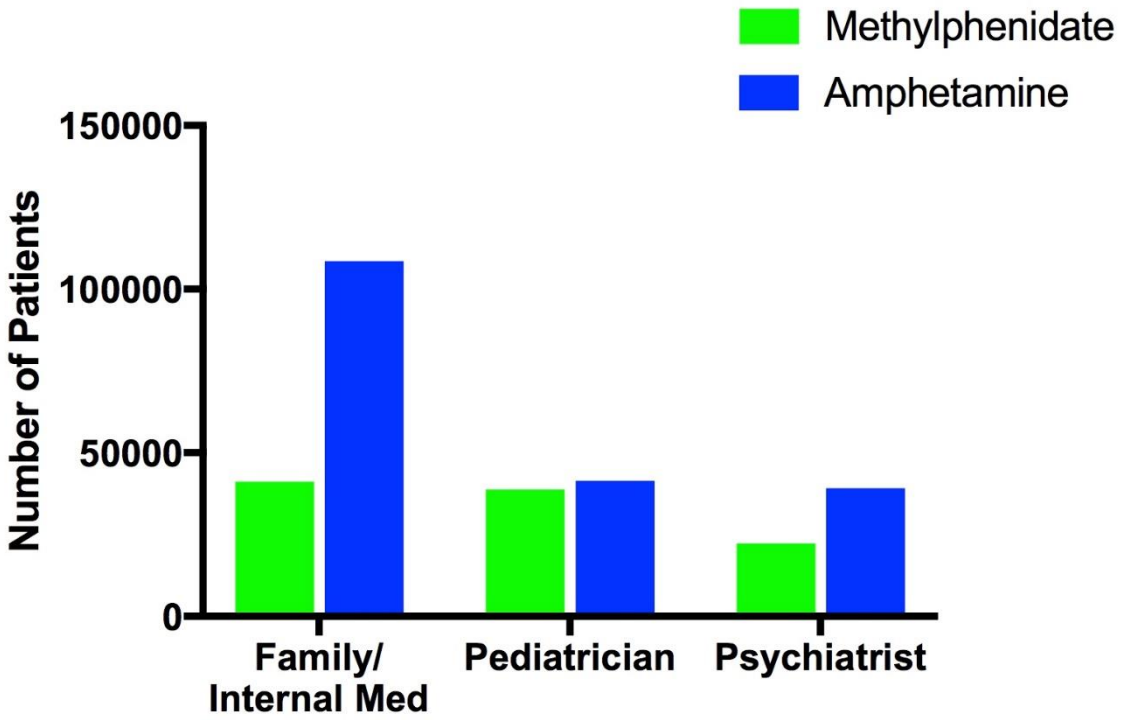
Moran LV et al., *N Engl J Med*, 2019, 380(12): 1128-38

Frequency of psychotic episodes

- Psychotic episodes occurred in **106** patients (0.10%) started on methylphenidate vs. **237** (0.21%) amphetamine in PS-matched patients
- Short follow-up time:
  - Median duration of F/U **~ 4-5 months**
  - Patients censored after stopping stimulant
- Psychotic diagnosis AND antipsychotic Rx
  - **77%** of episodes for **amphetamine** group INPATIENT
  - **62%** of episodes for **methylphenidate** group INPATIENT
- **Incidence** stopping maximal follow-up of 180 days of F/U:
  - Amphetamine: **323** per 100,000 person-years
  - Methylphenidate: **188** per 100,000 person-years
  - General population: **84*** per 100,000 person-years

*Randomly selected patients never prescribed stimulants matched on age, gender, year to PS-matched amphetamine group 4:1

Provider Type



Subgroup Analysis by Provider Type

	Methylphenidate		Amphetamine		
	Number of patients	No. Psychosis Events	Number of patients	No. Psychosis Events	Hazard Ratio (95% CI)
Family/Internal Medicine	41,165	32	108,584	207	**1.78** (1.21, 2.62)
Pediatrician	38,842	30	41,464	64	**1.70** (1.09, 2.67)
Psychiatrist	22,349	37	39,201	112	**1.38** (0.93, 2.04)

Sensitivity Analyses

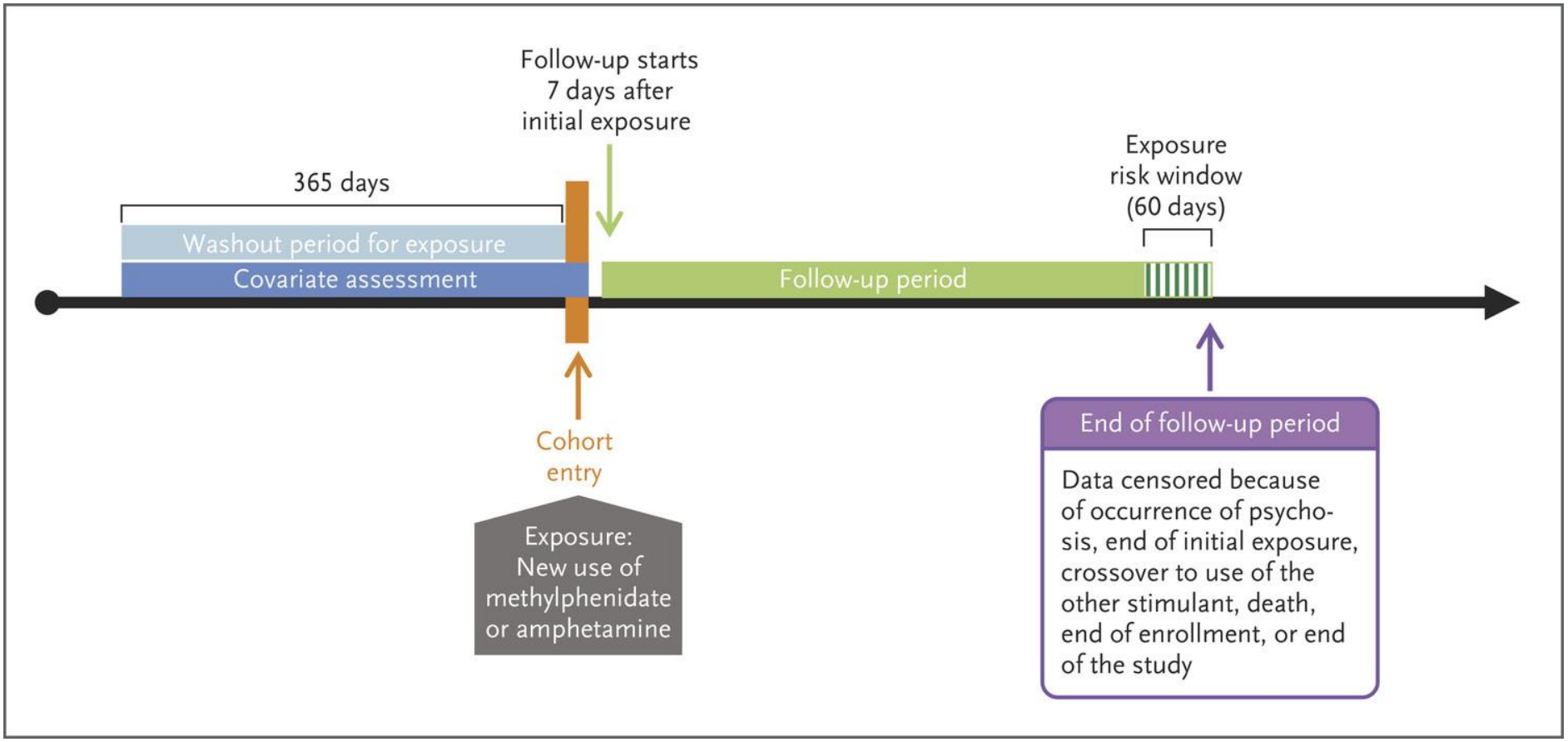
Ruling out alternative explanations:

- Did patients prescribed amphetamines have more severe **psychiatric comorbidity** not captured by claims data?
- **Negative control analysis:**
  - ED/Inpatient MDD *without* psychotic features:
    - **1.03** (0.84, 1.27)

Ruling out alternative explanations:

- Did patients prescribed amphetamines have **greater severity of ADHD**?
  - Perhaps adolescents/young adults diagnosed with ADHD with cognitive deficits related to prodrome preferentially prescribed amphetamines
  - If this was the case, we would expect to see greater severity of psychosis in amphetamine group well after stopping exposure to stimulant
- Modified Exposure Risk Window
  - 30 days: **1.74** (1.32, 2.31)
  - 60 days: **1.65** (1.31, 2.09)
  - 90 days: **1.58** (1.29, 1.95)
- Comparison with patients not treated with stimulants with ADHD
  - *Caution*: Confounding by contraindication – low power, more psychiatric and substance use disorders, PS matching suboptimal
    - Amphetamine vs. no stimulants: HR **1.70** (1.31 to 2.08)
    - Methylphenidate vs. no stimulants: HR **1.32** (0.91 to 1.72)

Overview of Study Design



Ruling out alternative explanations:

- Did patients prescribed amphetamines have **greater severity of ADHD**?
  - Perhaps adolescents/young adults diagnosed with ADHD with cognitive deficits related to prodrome preferentially prescribed amphetamines
  - If this was the case, we would expect to see greater severity of psychosis in amphetamine group well after stopping exposure to stimulant
- Modified Exposure Risk Window
  - 30 days: **1.74** (1.32, 2.31)
  - 60 days: **1.65** (1.31, 2.09)
  - 90 days: **1.58** (1.29, 1.95)
- Comparison with patients not treated with stimulants with ADHD
  - *Caution*: Confounding by contraindication – low power, more psychiatric and substance use disorders, PS matching suboptimal
    - Amphetamine vs. ADHD no stimulants: HR **1.70** (1.31 to 2.08)
    - Methylphenidate vs. ADHD no stimulants: HR **1.32** (0.91 to 1.72)

Ruling out alternative explanations:

- Were patients prescribed amphetamines more likely to be **abusing other substances** that led to increased psychosis?
- **Negative control analyses:**
  - ED/Inpatient Substance Use Disorders, Alcohol, Cannabis, Opioid Use Disorders as Outcomes
    - Effect sizes ranged from **0.91** to **1.12**, not significant
- **Bias analysis:**
  - Using data from National Survey on Drug Use on Health, estimated cannabis use in past month at 12.9%
  - Patients with ADHD have 2.78 increased risk of cannabis use: estimate prevalence of cannabis use in methylphenidate at **35.8%**
  - Increased risk of psychotic disorders with any cannabis use: RR 2.0
  - Prevalence of cannabis use in amphetamine users would have to be **97%** to fully explain findings

Lee et al., *Clin Psychol Rev* 2011;31(3):328–41.
Marconi et al., *Schizophr Bull* 2016;42(5):1262–9

Ruling out alternative explanations:

- Were patients prescribed amphetamines more likely to **abuse stimulants**?
  - IR amphetamines most commonly diverted and abused drugs by college age students, most of whom are not prescribed stimulants
  - Rates of stimulant misuse/abuse in college students much higher than younger patients
  - If greater abuse/misuse of amphetamines vs methylphenidate driving effect, would expect to see greater effect size with college age than pre-college groups and those prescribed IR medications

Advokat et al, *J Am Coll Health*. 2008;56(6):601-606

Ruling out alternative explanations:

- Age subgroups:
  - Pre-college (age 13-17): **1.62** (1.24, 2.12)
  - College age (age 18-25): **1.41** (0.99, 2.00)
- Formulation type subgroups:
  - ER amphetamine vs. ER methylphenidate: **1.77** (1.30, 2.40)
  - Lisdexamfetamine vs. ER methylphenidate: **1.54** (1.10, 2.16)
  - IR amphetamine vs. IR methylphenidate: **1.32** (0.77, 2.29)
- Interpretation:
  - High rates of **diversion**, in particular IR amphetamines, in college students prescribed stimulants (18.6 to 61.7%)

Benson et al., *Clin Child Fam Psychol Rev* 2015; 18: 50-76
Aldridge et al., *Pharmacoeconomics* 2011; 29: 621-35
Garnier et al, J *Clin Psychiatry* 2010; 71: 262-9

Strengths & Limitations

- Strengths
  - Large sample size
  - Consistent findings in two healthcare databases
  - Incident user, active comparator designs less prone to bias
  - Propensity score matching → balanced groups on *measured* confounders
  - Outcome validation
  - Sensitivity analyses supported conclusions of primary analysis
- Limitations
  - Observational, non-randomized
  - Lack of detailed data on patients available in claims data
  - Unmeasured confounders:
    - Race/ethnicity
    - SES
    - Family history of psychiatric disorders
    - Substance use under-reported

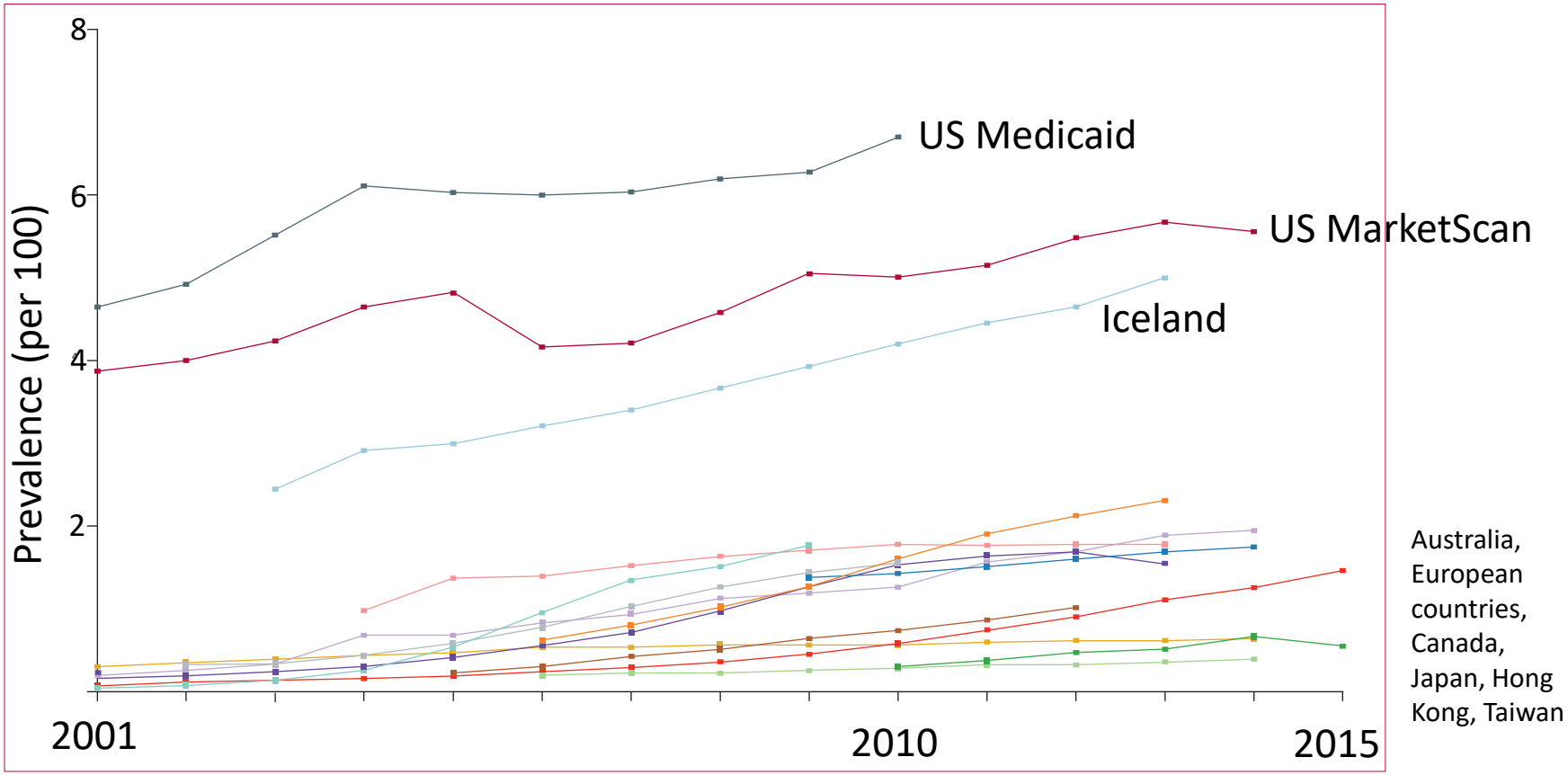
Effect on clinical practice?

- Events were rare
  - New users, early in treatment
- Recent network meta-analysis of RCT's of stimulants:
  - Recommends methylphenidate for adolescents
  - Amphetamines more effective in adults
  - Paucity of long-term data

- Rare event in setting of common exposure
  - Millions of patients in US currently prescribed amphetamines
  - Risk identified in this study translates to thousands of patients conferred undue risk
  - Alternative option available

Cortese et al., *Lancet Psychiatry* 2018; 5:727-38

Comparison of stimulant prescribing practices in different countries



Raman, et al., *Translational Psychiatry* 2018;5:824-835

Comparison of stimulant prescribing practices in different countries

Other countries

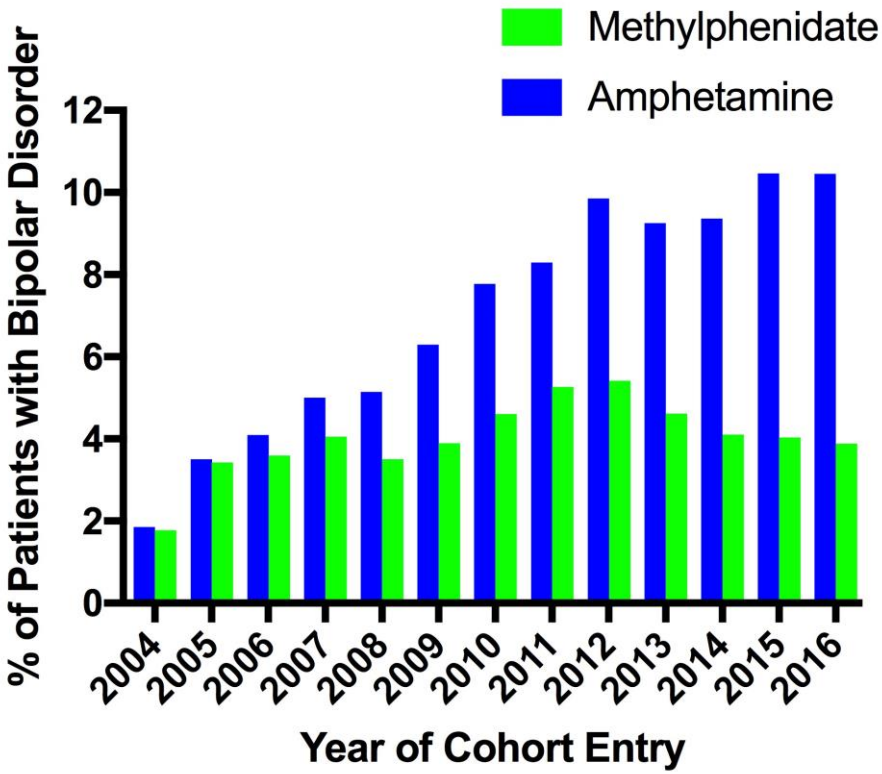
- Predominantly **methylphenidate**
- Hong Kong, Taiwan: only methylphenidate and atomoxetine are licensed for treatment of ADHD
- Japan: prescription amphetamines illegal
- Netherlands: 26 out of ~ 5000 patients prescribed amphetamine
- Nordic countries (adults): <1 to 4% prescribed amphetamine
- UK 2-3% amphetamine

United States

- **Amphetamine** use is common and growing
- U.S. is only country where amphetamines are used more than methylphenidate

Use of stimulants in bipolar disorder

- Swedish study:
  - Methylphenidate increased risk of mania in patients with bipolar affective disorder (BPAD) not concurrently taking mood stabilizers
  - Patients with BPAD on mood stabilizers were not at increased risk of mania after starting methylphenidate
- Lack of data on amphetamines:



Viktorin et al., *Am J Psychiatry*, 2017; 174(4):341-348

Future Directions

- Psychotic events rare
  - Identify patients most at risk
  - Patient characteristics
    - Depression
    - Family psych history
    - Co-morbid cannabis use
  - Prescribing patterns
    - Dose
    - Monitoring
    - High risk use (overlapping prescriptions, co-prescribing controlled substances)

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NARSAD Young Investigator

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Take-home points

- Prescription amphetamines are associated with an increased risk of psychosis compared with methylphenidate
- Study focused on psychotic episodes that occurred in early period of new use
- Psychotic events were rare overall