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

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Brain and Behavior Research Foundation
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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

<table>
<thead>
<tr>
<th></th>
<th>Not exposed (n=123)</th>
<th>Exposed (n=82)</th>
<th>Test statistic</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>38.1 ± 12.6</td>
<td>28.0 ± 9.5</td>
<td>t=-6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (M)</td>
<td>74 (60.2%)</td>
<td>62 (75.6%)</td>
<td>X²=5.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Diagnosis:</td>
<td></td>
<td></td>
<td>X²=7.8</td>
<td>0.10</td>
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<tr>
<td>Schizophrenia</td>
<td>73 (59.4%)</td>
<td>37 (45.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAD</td>
<td>39 (31.7%)</td>
<td>34 (41.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPAD</td>
<td>1 (0.8%)</td>
<td>2 (2.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD</td>
<td>3 (2.4%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOS</td>
<td>7 (5.7%)</td>
<td>9 (11.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-degree relative</td>
<td>17 (13.8%)</td>
<td>6 (7.3%)</td>
<td>X²=2.1</td>
<td>0.15</td>
</tr>
<tr>
<td>Education</td>
<td>13.8 ± 2.4</td>
<td>13.5 ± 2.4</td>
<td>t=0.8</td>
<td>0.41</td>
</tr>
<tr>
<td>IQ</td>
<td>108.8 ± 8.4</td>
<td>107.7 ± 9.4</td>
<td>t=0.66</td>
<td>0.51</td>
</tr>
<tr>
<td>Cannabis</td>
<td>39 (31.7%)</td>
<td>52 (63.4%)</td>
<td>X²=20.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other substance use</td>
<td>20 (16.3%)</td>
<td>22 (26.8%)</td>
<td>X²=20.0</td>
<td>0.07</td>
</tr>
</tbody>
</table>
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

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

At risk

Howes O. Arch Gen Psychiatry 2012

Howes O. Arch Gen Psychiatry 2009

Similar findings in mania with psychotic features
Dopamine Transporter Availability

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

Howes O. *Arch Gen Psychiatry* 2012
Hypothesis: amphetamine associated with greater risk of psychosis than methylphenidate

<table>
<thead>
<tr>
<th></th>
<th>Presynaptic DA release</th>
<th>Dopamine transporter inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia/Psychosis</td>
<td>↑↑↑</td>
<td>-</td>
</tr>
<tr>
<td>Stimulants used for ADHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphetamines</td>
<td>↑↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>↑</td>
<td>↑↑↑↑</td>
</tr>
</tbody>
</table>
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 Clininformatics**
  – 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

365 days

Washout period for exposure

Covariate assessment

Follow-up starts 7 days after initial exposure

Exposure risk window (60 days)

Follow-up period

End of follow-up period

Data censored because of occurrence of psychosis, end of initial exposure, crossover to use of the other stimulant, death, end of enrollment, or end of the study

Cohort entry

Exposure: New use of methylphenidate or 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%

<table>
<thead>
<tr>
<th></th>
<th>Psychotic</th>
<th>Not Psychotic</th>
<th>Total</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 psychosis code +Rx</td>
<td>27</td>
<td>2</td>
<td>29</td>
<td>93.1%</td>
</tr>
<tr>
<td>1 psychosis code -Rx</td>
<td>14</td>
<td>22</td>
<td>36</td>
<td>38.9%</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>24</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>

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

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

2005 - 2006

2013 - 2014
Results
<table>
<thead>
<tr>
<th></th>
<th>METHYL (N=33,825)</th>
<th>AMPH (N=33,825)</th>
<th>SMD</th>
<th>METHOD (N=77,098)</th>
<th>AMPH (N=77,098)</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>17.0 ± 3.2</td>
<td>17.0 ± 3.1</td>
<td>0.04</td>
<td>17.1 ± 3.2</td>
<td>17.1 ± 3.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12,681 (37.5%)</td>
<td>12,633 (37.3%)</td>
<td>0.004</td>
<td>28,737 (37.3%)</td>
<td>28,678 (37.1%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>3,071 (9.1%)</td>
<td>3,047 (9.0%)</td>
<td>0.017</td>
<td>13,326 (17.3%)</td>
<td>13,210 (17.1%)</td>
<td>0.010</td>
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<tr>
<td>North Central</td>
<td>9,890 (29.2%)</td>
<td>10,028 (29.6%)</td>
<td></td>
<td>23,458 (30.4%)</td>
<td>23,582 (30.6%)</td>
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<tr>
<td>South</td>
<td>16,455 (48.6%)</td>
<td>16,359 (48.4%)</td>
<td></td>
<td>28,295 (36.7%)</td>
<td>28,151 (36.5%)</td>
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</tr>
<tr>
<td>West</td>
<td>4,378 (12.9%)</td>
<td>4,364 (12.9%)</td>
<td></td>
<td>11,158 (14.5%)</td>
<td>11,257 (14.6%)</td>
<td></td>
</tr>
<tr>
<td>ADHD Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># outpatient</td>
<td>2.2 ± 3.5</td>
<td>2.2 ± 5.0</td>
<td>0.001</td>
<td>2.2 ± 4.0</td>
<td>2.2 ± 4.7</td>
<td>0.002</td>
</tr>
<tr>
<td>ODD/Conduct</td>
<td>1,808 (5.3%)</td>
<td>1,804 (5.3%)</td>
<td>0.001</td>
<td>3,413 (4.4%)</td>
<td>3,434 (4.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>2,229 (6.6%)</td>
<td>2,238 (6.6%)</td>
<td>0.001</td>
<td>4,727 (6.1%)</td>
<td>4,775 (6.2%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Psychiatric Comorbidity</td>
<td>OPTUM CLINFORMATICS After Propensity-Score Matching</td>
<td>MARKETSCAN After Propensity-Score Matching</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>----------------------------------------------------</td>
<td>--------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>METHYL (N=33,825)</td>
<td>AMPH (N=33,825)</td>
<td>SMD</td>
<td>METHYL (N=77,098)</td>
<td>AMPH (N=77,098)</td>
<td>SMD</td>
</tr>
<tr>
<td>Depression</td>
<td>6,394 (18.9%)</td>
<td>6,478 (19.2%)</td>
<td>0.006</td>
<td>12,307 (16.0%)</td>
<td>12,434 (16.1%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Anxiety/PTSD</td>
<td>4,391 (13.0%)</td>
<td>4,405 (13.0%)</td>
<td>0.001</td>
<td>8,698 (11.3%)</td>
<td>8,673 (11.2%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>5,245 (15.5%)</td>
<td>5,308 (15.7%)</td>
<td>0.005</td>
<td>11,439 (14.8%)</td>
<td>11,527 (15.0%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>1,025 (3.0%)</td>
<td>1,066 (3.2%)</td>
<td>0.007</td>
<td>2,443 (3.2%)</td>
<td>2,437 (3.2%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Prescription Opioid Use</td>
<td>4,865 (14.4%)</td>
<td>4,875 (14.4%)</td>
<td>0.001</td>
<td>10,870 (14.1%)</td>
<td>10,809 (14.0%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Substance abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol use disorder or Rx</td>
<td>485 (1.4%)</td>
<td>507 (1.5%)</td>
<td>0.005</td>
<td>859 (1.1%)</td>
<td>879 (1.1%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cannabis use disorder</td>
<td>478 (1.4%)</td>
<td>490 (1.4%)</td>
<td>0.003</td>
<td>786 (1.0%)</td>
<td>797 (1.0%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Amphetamine associated with increased risk of psychosis compared with methylphenidate

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

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%
B Prescription of Stimulant and Number of Psychotic Episodes According to Year of Cohort Entry

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

Number of Patients

- Methylphenidate
- Amphetamine

- Family/Internal Med
- Pediatrician
- Psychiatrist

Number of Patients:
0 50000 100000 150000
# Subgroup Analysis by Provider Type

<table>
<thead>
<tr>
<th>Provider Type</th>
<th>Methylphenidate</th>
<th>Amphetamine</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family/Internal Medicine</td>
<td>41,165</td>
<td>108,584</td>
<td>1.78 (1.21, 2.62)</td>
</tr>
<tr>
<td>Pediatrician</td>
<td>38,842</td>
<td>41,464</td>
<td>1.70 (1.09, 2.67)</td>
</tr>
<tr>
<td>Psychiatrist</td>
<td>22,349</td>
<td>39,201</td>
<td>1.38 (0.93, 2.04)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Provider Type</th>
<th>Number of patients</th>
<th>No. Psychosis Events</th>
<th>Number of patients</th>
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<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
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<tr>
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<tr>
<td>Pediatrician</td>
<td>38,842</td>
<td>30</td>
<td>41,464</td>
<td>64</td>
<td>1.70 (1.09, 2.67)</td>
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<tr>
<td>Psychiatrist</td>
<td>22,349</td>
<td>37</td>
<td>39,201</td>
<td>112</td>
<td>1.38 (0.93, 2.04)</td>
</tr>
</tbody>
</table>
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

- **365 days**
  - Washout period for exposure
  - Covariate assessment

- **FOLLOW-UP PERIOD**
  - Follow-up starts 7 days after initial exposure

- **Exposure risk window (60 days)**

- **End of follow-up period**
  - Data censored because of occurrence of psychosis, end of initial exposure, crossover to use of the other stimulant, death, end of enrollment, or end of the study

- **Cohort entry**
  - Exposure: New use of methylphenidate or amphetamine
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

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., *Pharmacoconomics* 2011; 29: 621-35
Strengths & Limitations

- **Strengths**
  - Large sample size
  - Consistent findings in two healthcare databases
  - Incident user, active comparator designs less prone to bias
  - Propensity score matching \( \rightarrow \) 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:

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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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.