MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Effects of ADHD Medications on Functional Outcomes: A Systematic Literature Review & Meta-Analysis

Ronna Fried, Ed.D.
Director of Neuropsychology in the Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD, Massachusetts General Hospital
Assistant Professor in Psychology, Harvard Medical School

Disclosures

I have the following relevant financial relationship with a commercial interest to disclose:

Grant Support: Tris Pharmaceuticals

Past Support: Shire,NIH; FDA; Lundbeck

ADHD is a Prevalent and Morbid Disorder

- Estimated up to 11% of children and 5% of adults
- Associated with high rates of adverse functional outcomes including:
  - comorbid psychiatric disorders
  - academic impairments
  - accidents and injuries
  - car accidents
  - and many others

Stimulant Treatment Shown to Improve Core Symptoms but…

- There is limited information on the effects of stimulant medication on ADHD-associated functional impairments
- Such information is critical for the careful examination of the risks vs. benefits calculus when considering medication treatments for ADHD

Recently Large Datasets and Registries

- have examined the effects of medication for ADHD on ADHD-associated functional outcomes
- offered unique opportunity to gain new insights into the impact of these medications on ecologically valid indices of functional impairment.
- Compared with clinical trials, these studies provide information about the broader benefits of ADHD medications on ADHD-associated functional impairments and outcomes,
- also provide information on the full range of ADHD patients, not only those eligible for clinical trials.

Main Aim and Study Hypothesis

- To evaluate the available body of knowledge on the impact of stimulants on functional outcomes
- To this we conducted a systematic review and meta-analysis of the available literature from large databases examining the effects of stimulant treatment on ADHD-associated functional outcomes
- We hypothesized that this literature would show that ADHD medications improve important ADHD-associated serious and morbid functional outcomes

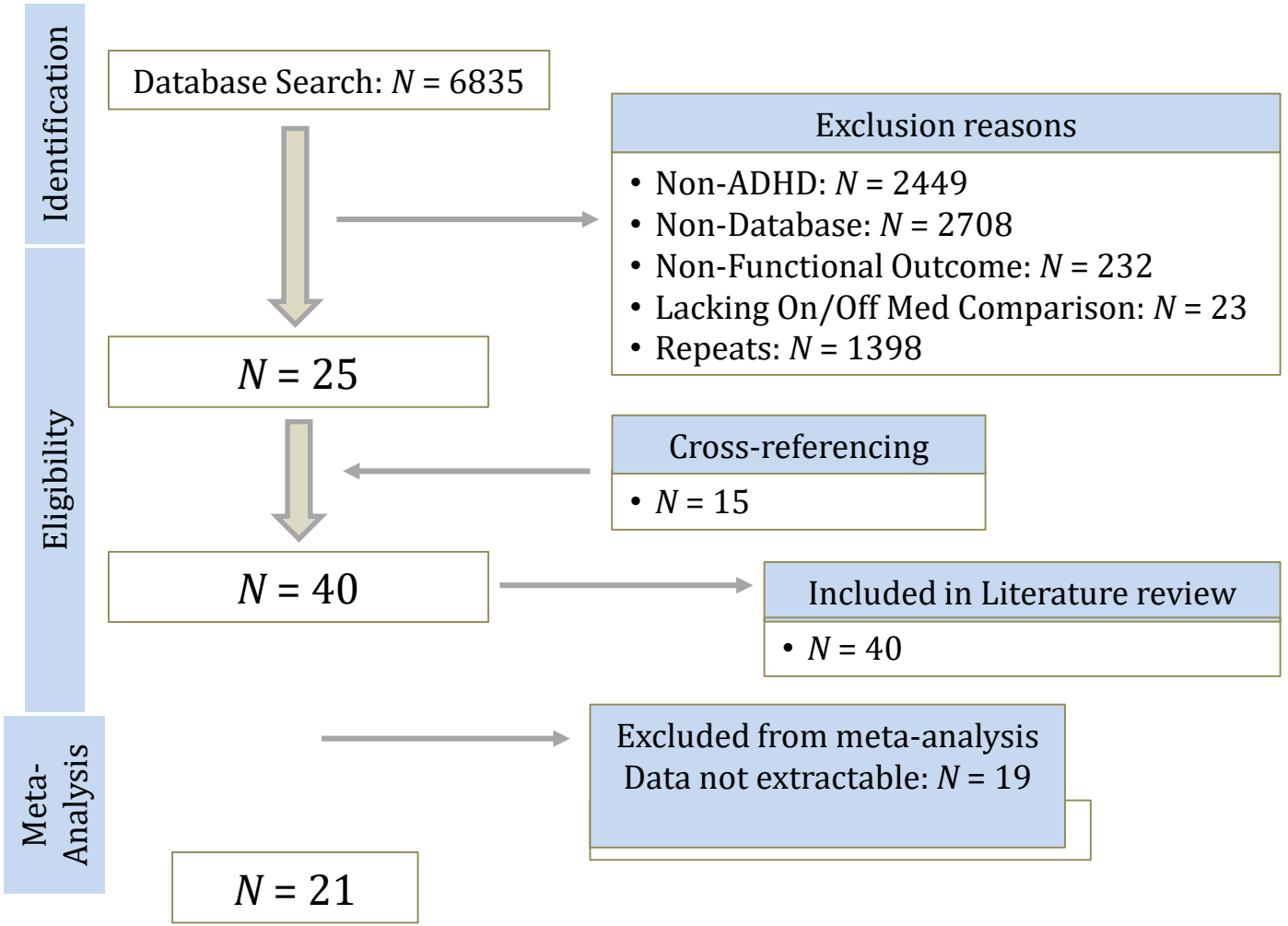
Advantages of Population-Based Datasets

- Very large datasets (up to 100 million people) (median CT=387)
- Clinical outcomes and treatment databases are linked
- Provides ecologically informative evidence on the impact of diseases and their treatment in the population

Literature Search

- A literature search was performed in PubMed, PsycINFO, MEDLINE, and Web of Science for articles published prior to January 1st, 2019
- Inclusion Criteria:
  - Study's main focus was on ADHD
  - Study relied on population-wide registries or large health insurance claim datasets
  - Main outcomes were functional outcomes
  - Data included information on treated vs. untreated ADHD individuals

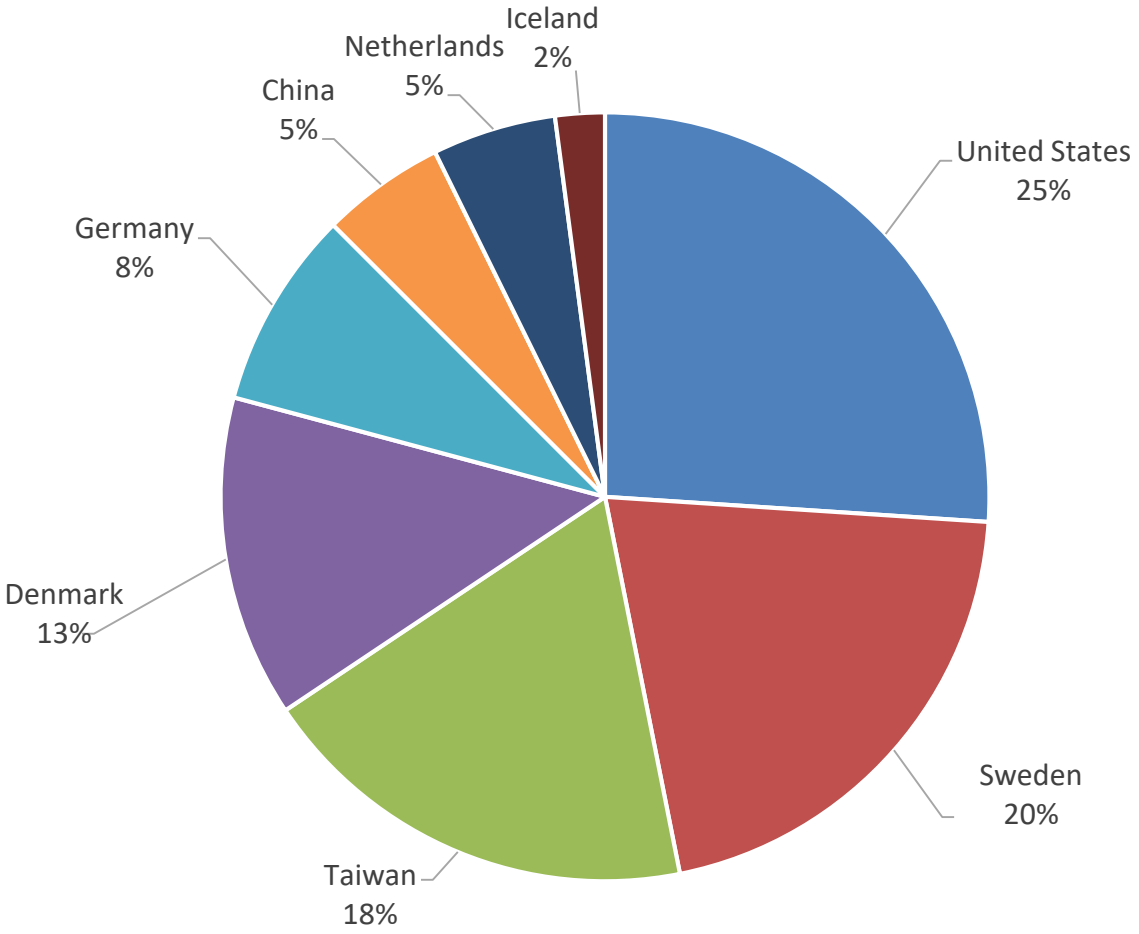
Prisma Diagram



Literature Search

- The initial search yielded > 6,000 scientific articles
- N=25 met our inclusion and exclusion criteria
- N=15 additional articles were identified through cross-referencing
- **Final sample for analysis included N=40 scientific articles**
- Of these, 21 articles had the necessary information to perform a meta analysis

Countries Contributing Datasets



Effects of ADHD Medications on Subsequent Functional Outcomes

- N= 4 mood disorders (depression and bipolar disorder)
- N= 4 substance use disorders (SUD)
- N= 3 criminality
- N= 3 suicidality
- N= 2 TBI
- N= 2 motor vehicle crash (MVC)
- N= 14 accidents and injuries
- N= 8 academic outcomes

Results

Mood Disorders

- 3 of 4 studies (N=254,752) showed that stimulant medication treatment was associated with a **significantly reduced risk** of developing mood disorders (depression and bipolar disorder)
- 1 of 4 studies (N=22,452) showed ADHD medication was associated with an increase risk for depression

Jerrell et al., 2015; Chang et al., 2016; Lee et al., 2016; Wang et al., 2016

Substance Use Disorders (SUDs)

- 3 of 4 studies (N=3,053,382) showed that stimulant medication treatment was associated with a **significantly reduced risk** of substance use outcomes
- 1 of 4 studies (N=9,424) found neither increased nor decreased impact of stimulant medication treatment on drug use disorders (a neutral effect)

Chang et al., 2014; Steinhausen & Bisgaard, 2014; Sundquist et al., 2015; Quinn et al., 2017

Criminality

- All three studies (N=34,443) that examined ADHD-associated criminality found that ADHD medication treatments, mostly stimulants, were associated with **significantly decreased rates** of criminal activity and contact with the justice system

Lichtenstein et al., 2012; Dalsgaard et al., 2014; Mohr-Jensen et al., 2019

Suicidality

- In all three studies (N=148,463) that examined the risk for suicidality, ADHD medications (mostly stimulants) were associated with a **reduced risk** of suicide attempts

Chen et al., 2014; Man et al., 2017; Liang et al., 2018

Traumatic Brain Injury (TBI)

- The two studies (N=121,979) that examined ADHD-associated TBIs reported that stimulant medication treatment was associated with a **significantly reduced risk** of TBI

Liao et al., 2018; Liou et al., 2018

Motor Vehicle Crashes (MVCs)

- The two studies that included over 2 million individuals examined the impact of ADHD medication treatment on MVC rates found a **significantly reduced risk** of MVCs for individuals when taking medication

Chang et al, 2014; Chang et al., 2017

Accident, Injuries, Emergency Room (ER) Visits

- 10 of 14 studies (N=134,793) that examined the impact of ADHD medications on the risk of accidents and injuries, found that medication treatment (mostly stimulants) was associated with **a reduced risk** of fractures, general injuries, insurance claims for injuries, and emergency room visits
- 4 of 14 Studies (N=30,856) found ADHD medication treatment had a neutral effect on accidents and injuries

Swensen et al., 2004; Leibson et al., 2006; Marcus et al., 2008; Merrill et al., 2009; Raman et al., 2013; van den Ban et al., 2014; Mikolajczyk et al., 2015; Man et al., 2015; Dalsgaard et al., 2015; Merrill et al., 2016; Lange et al., 2016; Jabob & Jostev, 2017; Chien et al., 2017; Chen et al., 2017.

Academic Outcomes

- 5 of 8 studies (N=43,203) found that ADHD medication treatments were associated with **significantly higher scores** on tests, **significant improvements** in grade point averages, **significantly fewer days absent** from school, and **significant improvements** in reading
- 3 of 8 studies (N=8765) did not show improvement in academic performance

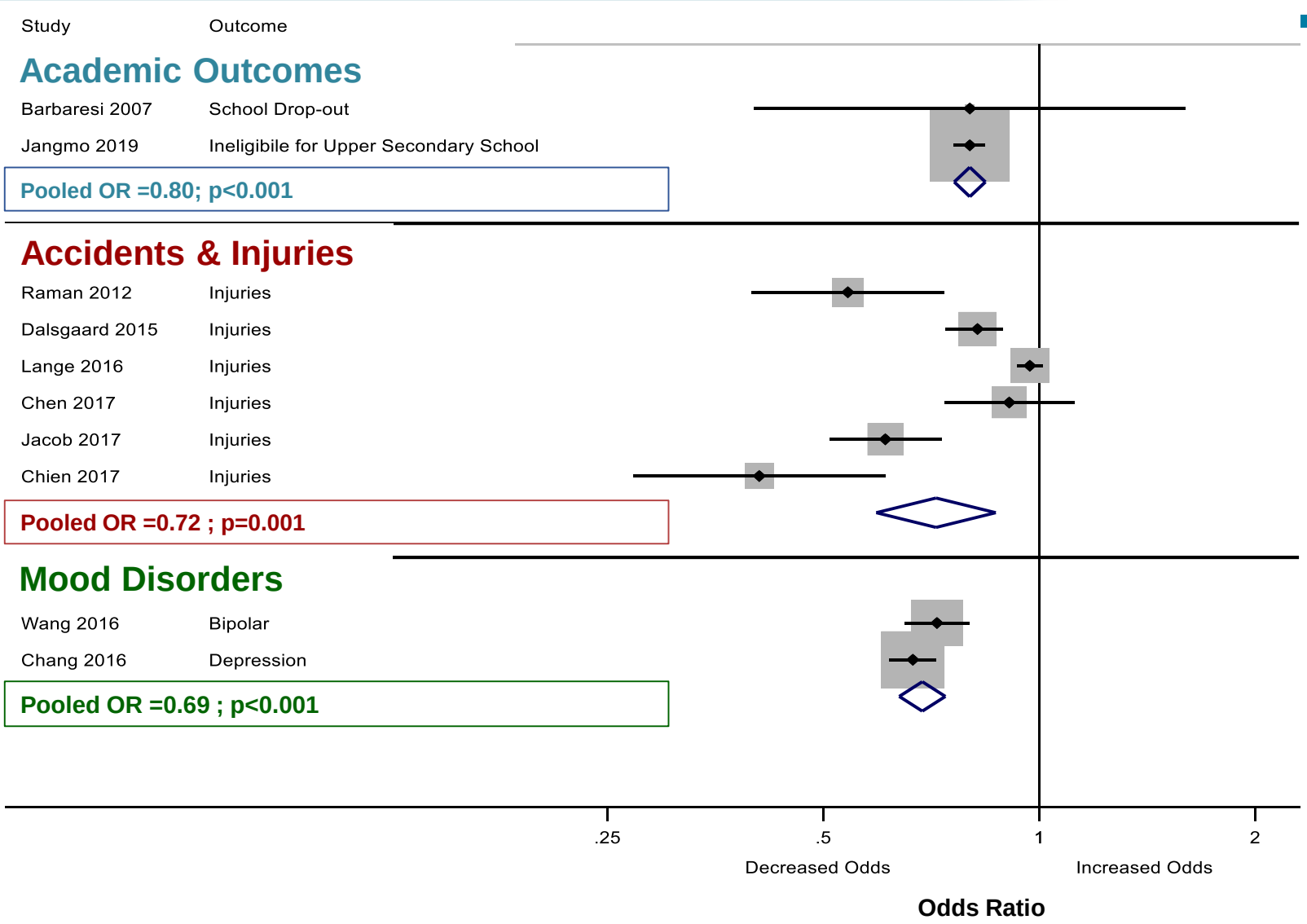
Barbaresi et al., 2007; Marcus & Durkin et al., 2011; Zoega et al., 2012; Currie et al., 2014; van der Schans et al., 2017; Lu et al., 2017; Keilow et al., 2018; Jangmo et al., 2019

Meta Analysis Results

Meta-Analysis Results

- Of the 40 articles identified, ***21 had extractable data for a meta-analysis of functional outcomes in medicated versus unmedicated ADHD subjects***

Meta-analyses of Functional Outcomes in Studies Reporting Odds Ratios (OR)



Meta-Analysis Findings: Odd Ratios (OR)

- Among the 14 studies that reported ORs, the pooled OR was <1 and **significant**, indicating that medicated ADHD subjects were at **significantly decreased odds** of developing poor functional outcomes when taking the medication compared to times when the ADHD individual was unmedicated

Summary of Results

- The majority of the N=40 articles identified document **a robust protective effect of ADHD medications** on **mood disorders, suicidality, criminality, substance use disorders, accidents and injuries, traumatic brain injuries, motor vehicle crashes, and educational outcomes**
- Similarly, the meta-analyses demonstrated an overall protective effect of medication treatment on these functional outcomes

Conclusions

- ADHD medication treatments are associated with decreases in the risks for a wide range of ADHD-associated functional outcomes supporting efforts aimed at early diagnosis and treatment of individuals with ADHD

Journal of Psychiatric Research 123 (2020) 21–30

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

A literature review and meta-analysis on the effects of ADHD medications on functional outcomes

Heidi Boland[a], Maura DiSalvo[a], Ronna Fried[a], K. Yvonne Woodworth[a], Timothy Wilens[b], Stephen V. Faraone[c], Joseph Biederman[b,*]

[a] Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD, Massachusetts General Hospital, Boston, MA, USA
[b] Department of Psychiatry, Harvard Medical School, Boston, MA, USA
[c] Departments of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY, USA

ARTICLE INFO

Keywords:
ADHD
Stimulants
Functional outcomes
Medication adherence

ABSTRACT

Objective: To conduct a systematic review and meta-analysis of literature from large databases and registries to assess the effects of ADHD medication on associated functional outcomes.
Study design: A literature search was performed in PubMed, PsycINFO, MEDLINE, and Web of Science for articles published prior to January 2019. Sample size, age range, country of origin, medication type, number of functional events and non-events, odds ratios and hazard ratios, and means and standard deviations were extracted. Random-effects meta-analyses were conducted for 21 studies examining functional outcomes.
Results: 40 articles were included. The majority suggest a robust protective effect of ADHD medication treatment on mood disorders, suicidality, criminality, substance use disorders, accidents and injuries, traumatic brain injuries, motor vehicle crashes, and educational outcomes. Similarly, the meta-analyses demonstrated a protective effect of medication treatment on academic outcomes, accidents and injuries, and mood disorders.
Conclusions: These findings suggest that ADHD medication treatments are associated with decreases in the risks for a wide range of ADHD-associated functional outcomes supporting efforts aimed at early diagnosis and treatment of individuals with ADHD.